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**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

ABBVIE INC. and GENENTECH, INC.,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, INC.,

Defendant.

**Civil Action No.** \_\_\_\_\_

**COMPLAINT FOR  
PATENT INFRINGEMENT**

**(Filed Electronically)**

Plaintiffs AbbVie Inc. ("AbbVie") and Genentech, Inc. ("Genentech") (collectively, "Plaintiffs"), by their undersigned attorneys, bring this action against Defendant Dr. Reddy's Laboratories, Inc. ("DRLI" or "Defendant") and hereby allege as follows:

**NATURE OF THE ACTION**

1. This action for patent infringement, brought pursuant to the patent laws of the United States, 35 U.S.C. §§ 1 *et seq.*, arises from DRLI's submission to the United States Food and Drug Administration ("FDA") of an Abbreviated New Drug Application ("ANDA")

No. 214733 (“DRL’s ANDA”) seeking approval to market a generic version of Plaintiffs’ highly successful pharmaceutical product VENCLEXTA<sup>®</sup>, prior to the expiration of the patents listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (an FDA publication commonly known as the “Orange Book”) for VENCLEXTA<sup>®</sup>. The Orange Book-listed patents are U.S. Patent Nos. 8,546,399 (“the ’399 Patent”), 9,174,982 (“the ’982 Patent”), 8,722,657 (“the ’657 Patent”), and 9,539,251 (“the ’251 Patent”). The ’399 Patent, the ’982 Patent, and the ’657 Patent are collectively referred to as “the Patents-in-suit.”

**PROCEEDING IN THE U.S. DISTRICT  
COURT FOR THE DISTRICT OF DELAWARE**

2. Plaintiffs filed a substantively similar suit on July 21, 2020 in the U.S. District Court for the District of Delaware (*AbbVie Inc., et al. v. Dr. Reddy’s Labs., Ltd., et al.*, Civil Action No. 20-968 (D. Del.)) against DRLI, along with DRLI’s parent, Dr. Reddy’s Laboratories, Ltd. (“DRLL”), an Indian company (DRLI and DRLL are collectively referred to as “DRL”), asserting infringement of the same three patents that are the subject of this suit (“the Delaware action”). The Delaware action is proceeding; service of the complaint, summons, and related papers has been initiated and Plaintiffs expect it to be completed by July 23, 2020.

3. On information and belief, the Court in the District of Delaware has jurisdiction over DRLI and venue is proper in that Judicial District, and, accordingly, the Delaware action should proceed. Out of an abundance of caution, however, Plaintiffs filed the instant suit in this Judicial District in the unlikely event that DRLI prevails in any challenge with respect to jurisdiction or venue in the Delaware action.

**VENCLEXTA<sup>®</sup>**

4. VENCLEXTA<sup>®</sup> (venetoclax) is a ground-breaking drug which has gained widespread acceptance in the medical community. It has been used to treat over 31,000 patients in the United States and around the world who suffer from chronic lymphocytic leukemia (“CLL”), small lymphocytic lymphoma (“SLL”), and, as part of a combination therapy, acute myeloid leukemia (“AML”).

5. VENCLEXTA<sup>®</sup> selectively targets and inhibits the B-cell CLL/lymphoma 2 (“BCL-2”) protein and is the first FDA-approved BCL-2 inhibitor. BCL-2 prevents apoptosis, or programmed cell death, which is the process for removal of aged or damaged cells.

6. VENCLEXTA<sup>®</sup> was first approved by the FDA on April 11, 2016 pursuant to New Drug Application (“NDA”) No. 208573. It is available as an oral tablet containing 10 mg, 50 mg, or 100 mg of venetoclax as the active pharmaceutical ingredient.

7. VENCLEXTA<sup>®</sup> is currently approved for use and indicated as follows: (1) for the treatment of adult patients with CLL or SLL; (2) in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

8. AbbVie and Genentech co-market and sell VENCLEXTA<sup>®</sup> in the United States and other parts of the world. They have invested hundreds of millions of dollars to discover venetoclax and develop VENCLEXTA<sup>®</sup>, including investing significant resources investigating whether VENCLEXTA<sup>®</sup> alone and in combination with other drugs can treat other types of cancer.

9. The FDA has recognized the innovative nature of VENCLEXTA<sup>®</sup> in granting it five breakthrough therapy designations: (1) treatment of patients with relapsed or refractory CLL who harbor the 17p deletion mutation; (2) treatment of patients with relapsed or refractory CLL in combination with the anti-CD20 antibody rituximab (Rituxan<sup>®</sup>); (3) venetoclax in combination with hypomethylating agents for the treatment of patients with untreated (treatment-naïve) AML who are ineligible to receive standard induction therapy (high-dose chemotherapy); (4) combination of venetoclax and low-dose cytarabine for treatment-naïve patients with AML, who are ineligible for intensive chemotherapy; and (5) venetoclax in combination with obinutuzumab for the treatment of adult patients with CLL. A breakthrough designation is reserved for a drug intended to treat a serious condition where preliminary clinical results indicate that the drug may demonstrate substantial improvement over available therapies.

10. VENCLEXTA<sup>®</sup> has one of the most robust clinical oncology development programs for a single molecule in the industry, with approximately 195 ongoing clinical trials (including 15 Phase 3 trials).

11. In addition to being well-received by the FDA and the medical community, VENCLEXTA<sup>®</sup> received the biomedical industry's highest accolade in 2017 when it was awarded the Prix Galien Award for Best Pharmaceutical Product.

### **THE PARTIES**

12. Plaintiff AbbVie is a corporation organized and existing under the laws of the state of Delaware, with its corporate headquarters at 1 North Waukegan Road, North Chicago, Illinois 60064. AbbVie is a global research and development-based biopharmaceutical company committed to developing innovative therapies for some of the world's most complex and critical conditions. The company's mission is to use its expertise, dedicated people, and unique approach to innovation to markedly improve treatments across therapeutic areas,



including in oncology. AbbVie holds NDA No. 208573 for VENCLEXTA<sup>®</sup> and is an assignee of all Patents-in-suit.

13. Plaintiff Genentech is a corporation organized under the laws of the State of Delaware, with its principal place of business at 1 DNA Way, South San Francisco, California 94080. Genentech is a biotechnology company dedicated to pursuing ground-breaking science to discover and develop medicines for people with serious and life-threatening diseases. Genentech is an assignee of the '399 and '982 Patents and an exclusive licensee of the '657 Patent.

14. On information and belief, Defendant DRLI is a corporation organized and existing under the laws of the State of New Jersey with its principal place of business at 107 College Road East, Princeton, New Jersey 08540.

15. On information and belief, DRLI is a wholly owned subsidiary of DRLL, a company organized and existing under the laws of India.

16. On information and belief, DRLI acts as DRLL's authorized agent in the United States.

17. On information and belief, DRLI is in the business of developing, manufacturing, and/or distributing generic drugs for marketing, sale, and/or use throughout the United States, including in this Judicial District.

18. On information and belief, and as described in DRL's written notification of DRL's ANDA and its accompanying § 505(j)(2)(A)(vii)(IV) certification received June 8, 2020 ("DRL's Notice Letter"), DRLI, acting in concert with or as an agent for DRLL, caused DRL's ANDA to be submitted to the FDA and seek FDA approval of DRL's ANDA prior to the expiration of the patents listed in the Orange Book for VENCLEXTA<sup>®</sup>.

19. On information and belief, DRLI, acting in concert with or as an agent for DRLL, intends to commercially manufacture, market, offer for sale, and sell the proposed generic venetoclax tablets described in DRL's ANDA ("DRL's Generic Version") throughout the United States, including in the State of New Jersey, in the event the FDA approves DRL's ANDA.

### **JURISDICTION & VENUE**

20. This civil action for patent infringement arises under the Patent Laws of the United States and the Food and Drug Laws of the United States, Titles 35 and 21, United States Code.

21. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

22. This Court has personal jurisdiction over DRLI by virtue of, *inter alia*, on information and belief, DRLI having availed itself of the rights and benefits of the laws of the State of New Jersey by engaging in substantial, continuous, and systematic contacts with the State of New Jersey and because DRLI intends to indirectly or directly market, sell, and/or distribute generic drugs to residents of this State, including DRL's Generic Version. Accordingly, DRLI should reasonably anticipate being hauled into court in this Judicial District.

23. On information and belief, Defendant, acting in concert with and/or as an agent for DRLL, filed DRL's ANDA.

24. On information and belief, DRLI, acting in concert with and/or as an agent for DRLL, will market, distribute, and/or sell DRL's Generic Version in the United States, including in New Jersey, upon approval of DRL's ANDA, and will derive substantial revenue from the sale of DRL's Generic Version.

25. On information and belief, DRL's Generic Version will be used within and throughout the United States, including in New Jersey.

26. On information and belief, DRL's Generic Version will be prescribed by physicians practicing in New Jersey, dispensed by pharmacies located within New Jersey, and used by patients in New Jersey.

27. This Court also has personal jurisdiction over Defendant by virtue of, *inter alia*, the fact that it has committed, aided, abetted, contributed to, and/or participated in the commission of a tortious act of patent infringement under 35 U.S.C. § 271(e)(2) that has led to and/or will lead to foreseeable harm and injury to Plaintiffs in New Jersey.

28. This Court also has personal jurisdiction over DRLI because, *inter alia*, DRLI, on information and belief, is registered as a manufacturer and wholesaler in New Jersey under license No. 5002312 and as a business operating in New Jersey under Business ID. No. 0100518911.

29. Venue is proper in this Judicial District for DRLI pursuant to 28 U.S.C. § 1400(b) because, on information and belief, *inter alia*, DRLI was incorporated in the State of New Jersey, DRLI has a regular and established place of business in the State of New Jersey, and DRL's Generic Version will be prescribed by physicians practicing in New Jersey, dispensed by pharmacies located within New Jersey, and used by patients in New Jersey. Each of these activities would have a substantial effect within New Jersey and would constitute an act of infringement of the Patents-in-suit if DRL's Generic Version is approved before the Patents-in-suit expire.

#### **THE ASSERTED PATENTS**

30. The '399 patent, titled "Apoptosis Inducing Agents for the Treatment of Cancer and Immune and Autoimmune Diseases," was duly and legally issued by the United

States Patent and Trademark Office (“USPTO”) on October 1, 2013. A true and correct copy of the ’399 patent is attached as Exhibit A.

31. The ’399 patent is assigned to AbbVie, Genentech, and the Walter and Eliza Hall Institute of Medical Research.

32. The ’982 patent, titled “Apoptosis-Inducing Agents for the Treatment of Cancer and Immune and Autoimmune Diseases,” was duly and legally issued by the USPTO on November 3, 2015. A true and correct copy of the ’982 patent is attached as Exhibit B.

33. The ’982 patent is assigned to AbbVie, Genentech, and the Walter and Eliza Hall Institute of Medical Research.

34. The ’657 patent, titled “Salts and Crystalline Forms of an Apoptosis-Inducing Agent,” was duly and legally issued by the USPTO on May 13, 2014. A true and correct copy of the ’657 patent is attached as Exhibit C.

35. The ’657 patent is assigned to AbbVie and exclusively licensed to Genentech.

#### **DRL’S ANDA**

36. On information and belief, DRL’s Notice Letter represents that DRLI, on behalf of DRLL, submitted and continues to maintain DRL’s ANDA to the FDA under 21 U.S.C. § 355(j).

37. On information and belief, and based on DRL’s Notice Letter, DRLI has submitted DRL’s ANDA to the FDA in order to obtain approval to engage in the commercial manufacture, use, or sale of venetoclax tablets as a purported generic version of VENCLEXTA<sup>®</sup> prior to the expiration of the Patents-in-suit and the ’251 Patent.

38. On information and belief, the FDA has not approved DRL’s ANDA.

39. DRL's Notice Letter states that "DRL seeks to obtain approval to engage in the commercial manufacture, use, or sale of" "venetoclax tablets, 10 mg, 50 mg, 100 mg." DRL's Notice Letter also states that "[t]he active ingredient present in [DRL's Generic Version] is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide), commonly known as venetoclax."

40. VENCLEXTA<sup>®</sup>'s Prescribing Information ("VENCLEXTA<sup>®</sup> PI") states that "VENCLEXTA<sup>®</sup> tablets for oral administration . . . contain 10, 50, or 100 mg venetoclax as the active ingredient" and "[v]enetoclax is described chemically as 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide)."

41. On information and belief, and as supported by DRL's Notice Letter, by filing DRL's ANDA, DRLI has certified to the FDA that DRL's Generic Version has the same active pharmaceutical ingredient as VENCLEXTA<sup>®</sup> and either the same or similar proposed labeling as VENCLEXTA<sup>®</sup>.

42. DRL's Notice Letter represents that DRLI certified in DRL's ANDA that the claims of the Patents-in-suit are invalid or would not be infringed by the commercial manufacture, use, sale, or offer for sale of DRL's Generic Version.

43. According to applicable regulations, Notice Letters such as DRL's Notice Letter must contain a detailed statement of the factual and legal bases for the applicant's opinion that the patent is invalid, unenforceable, or not infringed, which includes a claim-by-claim analysis, describing "[f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "[f]or each claim of a patent alleged to be

invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.” *See* 21 C.F.R. § 314.95(c)(7); *see also* 21 C.F.R. § 314.52.

44. For at least one claim of each of the ’399 and ’982 Patents, DRL’s Notice Letter failed to allege that DRL’s Generic Version or the proposed administration of DRL’s Generic Version would not meet the limitations of that claim.

45. DRL’s Notice Letter also fails to address the ’251 Patent, which is listed in the Orange Book for VENCLEXTA®.

46. DRL’s Notice Letter contained an Offer of Confidential Access (“OCA”) to certain confidential information regarding DRL’s Generic Version. Plaintiffs and DRLI subsequently exchanged proposed revisions to the draft OCA in an attempt to reach agreement on the terms for confidential access, but DRLI refused Plaintiffs’ reasonable requests, including requests for samples of DRL’s Generic Version and active pharmaceutical ingredient. Thus, as of the filing of this Complaint, the parties have not been able to reach an agreement.

47. To date, DRLI has not provided Plaintiffs with any portion of DRL’s ANDA nor any information regarding DRL’s Generic Version, beyond the information in DRL’s Notice Letter.

48. To date, DRLI has not provided Plaintiffs with samples of DRL’s Generic Version embodied by DRL’s ANDA or the active pharmaceutical ingredient.

49. The limited information relating to DRL’s Generic Version that was provided in DRL’s Notice Letter does not demonstrate that DRL’s Generic Version, which DRLI has asked the FDA to approve for sale in the U.S., will not fall within the scope of claims of the Patents-in-suit.

50. This action is being brought within 45 days of Plaintiffs' receipt on June 8, 2020 of DRL's Notice Letter, pursuant to 21 U.S.C. § 355(c)(3)(C). Accordingly, Plaintiffs are entitled to a stay of FDA approval pursuant to 21 U.S.C. § 355(j)(5)(B)(iii) and U.S.C. § 355(j)(5)(F)(ii).

**CLAIM FOR RELIEF**  
**COUNT 1: INFRINGEMENT OF THE '399 PATENT BY DRLI**

51. Plaintiffs restate, re-allege, and incorporate by reference paragraphs 1-50 as if fully set forth herein.

52. On information and belief, DRLI submitted or caused the submission of DRL's ANDA to the FDA, and thereby seeks FDA approval of DRL's Generic Version.

53. DRL's Generic Version infringes one or more claims of the '399 Patent.

54. DRLI did not contest infringement of any claim of the '399 Patent in DRL's Notice Letter. If DRLI had a factual or legal basis to contest infringement of the '399 Patent, it was required by applicable regulations to state such a basis in its Notice Letter. *See* 21 C.F.R. § 314.95(c)(7); *see also* 21 C.F.R. § 314.52.

55. DRLI has infringed one or more claims of the '399 Patent under 35 U.S.C. § 271(e)(2)(A) by submitting DRL's ANDA with Paragraph IV certification and thereby seeking FDA approval of a generic version of VENCLEXTA<sup>®</sup>, prior to the expiration of the '399 Patent.

56. On information and belief, the importation, manufacture, sale, offer for sale, or use of DRL's Generic Version prior to the expiration of the '399 Patent would infringe one or more claims of the '399 Patent under 35 U.S.C. § 271(a), and/or DRLI would induce or contribute to the inducement of the infringement of one or more claims of the '399 Patent under 35 USC § 271(b) and/or (c).

57. DRLI had actual and constructive notice of the '399 Patent prior to filing DRL's ANDA, and was aware that the filing of DRL's ANDA with the request for FDA approval prior to the expiration of the '399 Patent would constitute an act of infringement of the '399 Patent.

58. DRLI filed its ANDA without adequate justification for asserting that the '399 Patent is invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of DRL's Generic Version.

59. Plaintiffs will be irreparably harmed if DRLI is not enjoined from infringing, and from actively inducing or contributing to the infringement of, the '399 Patent. Plaintiffs do not have an adequate remedy at law and, considering the balance of hardships between Plaintiffs and DRLI, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

**CLAIM FOR RELIEF**  
**COUNT 2: INFRINGEMENT OF THE '982 PATENT BY DRLI**

60. Plaintiffs restate, re-allege, and incorporate by reference paragraphs 1-59 as if fully set forth herein.

61. On information and belief, DRLI submitted or caused the submission of DRL's ANDA to the FDA, and thereby seeks FDA approval of DRL's Generic Version.

62. DRL's Generic Version infringes one or more claims of the '982 Patent.

63. DRLI did not contest infringement of any claim of the '982 Patent in DRL's Notice Letter. If DRLI had a factual or legal basis to contest infringement of the '982 Patent, it was required by applicable regulations to state such a basis in its Notice Letter. *See* 21 C.F.R. § 314.95(c)(7); *see also* 21 C.F.R. § 314.52.



64. DRLI has infringed one or more claims of the '982 Patent under 35 U.S.C. § 271(e)(2)(A) by submitting DRL's ANDA with Paragraph IV certification and thereby seeking FDA approval of a generic version of VENCLEXTA<sup>®</sup>, prior to the expiration of the '982 Patent.

65. On information and belief, the importation, manufacture, sale, offer for sale, or use of DRL's Generic Version prior to the expiration of the '982 Patent would infringe one or more claims of the '982 Patent under 35 U.S.C. § 271(a), and/or DRLI would induce or contribute to the inducement of the infringement of one or more claims of the '982 Patent under 35 USC § 271(b) and/or (c).

66. DRLI had actual and constructive notice of the '982 Patent prior to filing DRL's ANDA, and was aware that the filing of DRL's ANDA with the request for FDA approval prior to the expiration of the '982 Patent would constitute an act of infringement of the '982 Patent.

67. DRLI filed its ANDA without adequate justification for asserting that the '982 Patent is invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of DRL's Generic Version.

68. Plaintiffs will be irreparably harmed if DRLI is not enjoined from infringing, and from actively inducing or contributing to the infringement of, the '982 Patent. Plaintiffs do not have an adequate remedy at law and, considering the balance of hardships between Plaintiffs and DRLI, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

**CLAIM FOR RELIEF**  
**COUNT 3: INFRINGEMENT OF THE '657 PATENT BY DRLI**

69. Plaintiffs restate, re-allege, and incorporate by reference paragraphs 1-68 as if fully set forth herein.

70. On information and belief, DRLI submitted or caused the submission of DRL's ANDA to the FDA, and thereby seeks FDA approval of DRL's Generic Version.

71. On information and belief, DRL's Generic Version infringes one or more claims of the '657 Patent.

72. DRLI has infringed one or more claims of the '657 Patent under 35 U.S.C. § 271(e)(2)(A) by submitting DRL's ANDA with Paragraph IV certification and thereby seeking FDA approval of a generic version of VENCLEXTA<sup>®</sup>, prior to the expiration of the '657 Patent.

73. On information and belief, the importation, manufacture, sale, offer for sale, or use of DRL's Generic Version prior to the expiration of the '657 Patent would infringe one or more claims of the '657 Patent under 35 U.S.C. § 271(a), and/or DRLI would induce or contribute to the inducement of the infringement of one or more claims of the '657 Patent under 35 USC § 271(b) and/or (c).

74. DRLI had actual and constructive notice of the '657 Patent prior to filing DRL's ANDA, and was aware that the filing of DRL's ANDA with the request for FDA approval prior to the expiration of the '657 Patent would constitute an act of infringement of the '657 Patent.

75. DRLI filed its ANDA without adequate justification for asserting that the '657 Patent is invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of DRL's Generic Version.

76. Plaintiffs will be irreparably harmed if DRLI is not enjoined from infringing, and from actively inducing or contributing to the infringement of, the '657 Patent. Plaintiffs do not have an adequate remedy at law and, considering the balance of hardships

between Plaintiffs and DRLI, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

**PRAYER FOR RELIEF**

**WHEREFORE**, Plaintiffs respectfully request the following relief:

A. A Judgment that DRLI has infringed each of the Patents-in-suit under 35 U.S.C. § 271(e)(2)(A);

B. A Judgment and Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any FDA approval of DRL's ANDA shall be no be earlier than the last expiration date of any of the Patents-in-suit, or any later expiration of exclusivity for the Patents-in-suit, including any extensions or regulatory exclusivities;

C. A Judgment and Order that DRLI, its directors, officers, agents, attorneys, affiliates, divisions, successors and employees, and those acting in privity or concert with them, are permanently enjoined from commercially manufacturing, using, offering to sell, selling, marketing, distribution, or importing DRL's Generic Version and any other product that infringes or induces or contributes to the infringement of one or more of the Patents-in-suit, prior to the expiration of the Patents-in-suit, including any exclusivities or extensions to which Plaintiffs are or become entitled;

D. A Judgment declaring that making, using, selling, offering to sell, or importing DRL's Generic Version, or inducing or contributing to such conduct, would constitute infringement of one or more of the Patents-in-suit pursuant to 35 U.S.C. § 271 (a), (b), and/or (c);

E. A declaration under 28 U.S.C. § 2201 that, if DRLI, its officers, agents, employees, parents, affiliates, and subsidiaries, and all persons and entities acting in concert with it or on its behalf, engage in the commercial manufacture, use, offer for sale, sale or importation

of DRL's Generic Version, it will constitute an act of infringement pursuant to 35 U.S.C. § 271 (a), (b), and/or (c);

F. An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if DRLI engages in the commercial manufacture, use, offer for sale, sale, and/or importation of DRL's Generic Version, or any product that infringes one or more Patents-in-suit, or induces or contributes to such conduct, prior to the expiration of the Patents-in-suit, including any additional exclusivity period applicable to those patents;

G. A finding that this case is an exceptional case and an award of attorneys' fees in this action pursuant to 35 U.S.C. § 285;

H. Costs and expenses in this action; and

I. Such other and further relief as this Court deems just and proper.

Dated: July 22, 2020

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**CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1**

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter captioned *AbbVie Inc., et al. v. Dr. Reddy's Labs., Ltd., et al.*, Civil Action No. 20-968 (D. Del.) is related to the matter in controversy because the matter in controversy involves the same Plaintiffs and the same patents, and because DRLI is seeking approval to market a generic version of the same pharmaceutical product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: July 22, 2020

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# EXHIBIT A

US008546399B2

(12) **United States Patent**  
**Bruncko et al.**

(10) **Patent No.:** **US 8,546,399 B2**  
(45) **Date of Patent:** **Oct. 1, 2013**

- (54) **APOPTOSIS INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE AND AUTOIMMUNE DISEASES**
- (75) Inventors: **Milan Bruncko**, Green Oaks, IL (US); **Hong Ding**, Gurnee, IL (US); **George A. Doherty**, Libertyville, IL (US); **Steven W. Elmore**, Northbrook, IL (US); **Lisa A. Hasvold**, Grayslake, IL (US); **Laura Hexamer**, Grayslake, IL (US); **Aaron R. Kunzer**, Schaumburg, IL (US); **Xiaohong Song**, Grayslake, IL (US); **Andrew J. Souers**, Evanston, IL (US); **Gerard M. Sullivan**, Lake Villa, IL (US); **Zhi-Fu Tao**, Gurnee, IL (US); **Gary T. Wang**, Libertyville, IL (US); **Le Wang**, Vernon Hills, IL (US); **Xilu Wang**, Grayslake, IL (US); **Michael D. Wendt**, Vernon Hills, IL (US); **Robert Mantei**, Franklin, WI (US); **Todd M. Hansen**, Grayslake, IL (US)

(73) Assignee: **Abbvie Inc.**, North Chicago, IL (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 284 days.

(21) Appl. No.: **12/787,682**

(22) Filed: **May 26, 2010**

(65) **Prior Publication Data**

US 2010/0305122 A1 Dec. 2, 2010

**Related U.S. Application Data**

(60) Provisional application No. 61/181,203, filed on May 26, 2009.

(51) **Int. Cl.**  
**A61K 31/407** (2006.01)  
**C07D 401/12** (2006.01)

(52) **U.S. Cl.**  
USPC ..... **514/252.18**; 544/362

(58) **Field of Classification Search**  
USPC ..... 544/362  
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are compounds which inhibit the activity of anti-apoptotic Bcl-2 proteins, compositions containing the compounds and methods of treating diseases during which is expressed anti-apoptotic Bcl-2 protein.

**24 Claims, No Drawings**



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# APOPTOSIS INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE AND AUTOIMMUNE DISEASES

This application claims priority to U.S. Provisional Application Ser. No. 61/181,203 filed May 26, 2009, which is incorporated by reference in its entirety.

## FIELD OF THE INVENTION

This invention pertains to compounds which inhibit the activity of Bcl-2 anti-apoptotic proteins, compositions containing the compounds, and methods of treating diseases during which anti-apoptotic Bcl-2 proteins are expressed.

## BACKGROUND OF THE INVENTION

Anti-apoptotic Bcl-2 proteins are associated with a number of diseases. There is therefore an existing need in the therapeutic arts for compounds which inhibit the activity of anti-apoptotic Bcl-2 proteins.

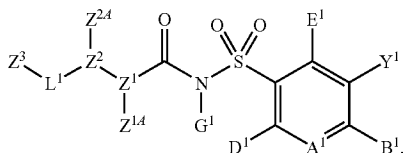
Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system.

Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, spleen cancer, and the like is described in commonly-owned PCT US 2004/36770, published as WO 2005/049593, and PCT US 2004/37911, published as WO 2005/024636.

Involvement of Bcl-2 proteins in immune and autoimmune diseases is described in *Current Allergy and Asthma Reports* 2003, 3, 378-384; *British Journal of Haematology* 2000, 110 (3), 584-90; *Blood* 2000, 95(4), 1283-92; and *New England Journal of Medicine* 2004, 351(14), 1409-1418. Involvement of Bcl-2 proteins in arthritis is disclosed in commonly-owned U.S. Provisional Patent Application Ser. No. 60/988,479. Involvement of Bcl-2 proteins in bone marrow transplant rejection is disclosed in commonly-owned U.S. patent application Ser. No. 11/941,196.

## SUMMARY OF THE INVENTION

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (I)



wherein

A¹ is N or C(A²);

A² is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC

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(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR¹,⁴;

B¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR¹,⁴;

D¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR¹,⁴;

E¹ is H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR¹,⁴; and

Y¹ is H, CN, NO₂, C(O)OH, F, Cl, Br, I, CF₃, OCF₃, CF₂CF₃, OCF₂CF₃, R¹⁷, OR¹⁷, C(O)R¹⁷, C(O)OR¹⁷, SR¹⁷, SO₂R¹⁷, NH₂, NHR¹⁷, N(R¹⁷)₂, NHC(O)R¹⁷, C(O)NH₂, C(O)NHR¹⁷, C(O)N(R¹⁷)₂, NHS(O)R¹⁷ or NHSO₂R¹⁷; or

E¹ and Y¹, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

(I) A², B¹, and D¹ are independently selected H, R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, C(O)R¹, C(O)OR¹, OC(O)R¹, NHR¹, N(R¹)₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHC(O)OR¹, NR¹C(O)OR¹, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, NR¹C(O)NHR¹, NR¹C(O)N(R¹)₂, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHSO₂R¹, NR¹SO₂R¹, NHSO₂NHR¹, NHSO₂N(R¹)₂, NR¹SO₂NHR¹, NR¹SO₂N(R¹)₂, C(O)NHNH₂, C(O)NHNOR¹, C(O)NHSO₂R¹, C(NH)NH₂, C(NH)NHR¹, C(NH)N(R¹)₂NHSO₂NHR¹, NHSO₂N(CH₃)R¹, N(CH₃)SO₂N(CH₃)R¹, F, Cl, Br, I, CN, NO₂, N₃, OH, C(O)H, CHNOH, CH(NOCH₃), CF₃, C(O)OH, C(O)NH₂ or C(O)OR¹,⁴; or

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$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$A^2$ ,  $D^1$ , and  $E^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$A^2$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$D^1$ ,  $E^1$ , and  $Y^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$A^2$  and  $D^1$ , together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$B^1$ ,  $E^1$ , and  $Y^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$G^1$  is H, or  $C(O)OR$ ;

R is alkyl;

$R^1$  is  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$ ;

$R^{1,4}$  is cycloalkyl, cycloalkenyl or cycloalkynyl;

$R^2$  is phenyl, which is unfused or fused with  $R^{2,4}$ ;  $R^{2,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^3$  is heteroaryl, which is unfused or fused with  $R^{3,4}$ ;  $R^{3,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^4$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{4,4}$ ;  $R^{4,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^5$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^6$ ,  $NC(R^{6A})(R^{6B})$ ,  $R^7$ ,  $OR^7$ ,  $SR^7$ ,  $S(O)R^7$ ,  $SO_2R^7$ ,  $NHR^7$ ,  $N(R^7)_2$ ,  $C(O)R^7$ ,  $C(O)NH_2$ ,  $C(O)NHR^7$ ,  $C(O)N(R^7)_2$ ,  $NHC(O)R^7$ ,  $NR^7C(O)R^7$ ,  $NHSO_2R^7$ ,  $NHC(O)OR^7$ ,  $SO_2NH_2$ ,  $SO_2NHR^7$ ,  $SO_2N(R^7)_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)$

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$NHR^7$ ,  $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$ ,  $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^7$ , OH, (O),  $C(O)OH$ ,  $N_3$ , CN,  $NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

$R^6$  is  $C_2$ - $C_5$ -spiroalkyl, each of which is unsubstituted or substituted with OH, (O),  $N_3$ , CN,  $CF_3$ ,  $CF_2CF_3$ , F, Cl, Br, I,  $NH_2$ ,  $NH(CH_3)$  or  $N(CH_3)_2$ ;

$R^{6A}$  and  $R^{6B}$  are independently selected alkyl or, together with the N to which they are attached,  $R^{6C}$ ;

$R^{6C}$  is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one  $CH_2$  moiety unreplaced or replaced with O,  $C(O)$ ,  $CNOH$ ,  $CNOCH_3$ , S,  $S(O)$ ,  $SO_2$  or  $NH$ ;

$R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$  or  $R^{11}$ ;

$R^8$  is phenyl, which is unfused or fused with  $R^{8,4}$ ;  $R^{8,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^9$  is heteroaryl, which is unfused or fused with  $R^{9,4}$ ;  $R^{9,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{10}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{10,4}$ ;  $R^{10,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{11}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{12}$ ,  $OR^{12}$ ,  $SR^{12}$ ,  $S(O)R^{12}$ ,  $SO_2R^{12}$ ,  $C(O)R^{12}$ ,  $CO(O)R^{12}$ ,  $OC(O)R^{12}$ ,  $OC(O)OR^{12}$ ,  $NH_2$ ,  $NHR^{12}$ ,  $N(R^{12})_2$ ,  $NHC(O)R^{12}$ ,  $NR^{12}C(O)R^{12}$ ,  $NHS(O)_2R^{12}$ ,  $NR^{12}S(O)_2R^{12}$ ,  $NHC(O)OR^{12}$ ,  $NR^{12}C(O)OR^{12}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{12}$ ,  $NHC(O)N(R^{12})_2$ ,  $NR^{12}C(O)NHR^{12}$ ,  $NR^{12}C(O)N(R^{12})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{12}$ ,  $C(O)N(R^{12})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{12}$ ,  $C(O)NHSO_2R^{12}$ ,  $C(O)NR^{12}SO_2R^{12}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{12}$ ,  $SO_2N(R^{12})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{12}$ ,  $C(N)N(R^{12})_2$ ,  $CNOH$ ,  $CNOCH_3$ , OH, (O), CN,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ , F, Cl, Br or I;

$R^{12}$  is  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$  or  $R^{16}$ ;

$R^{13}$  is phenyl, which is unfused or fused with  $R^{13,4}$ ;  $R^{13,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{14}$  is heteroaryl, which is unfused or fused with  $R^{14,4}$ ;  $R^{14,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{15}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with  $R^{15,4}$ ;  $R^{15,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{16}$  is alkyl, alkenyl or alkynyl;

$R^{17}$  is  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  or  $R^{21}$ ;

$R^{18}$  is phenyl, which is unfused or fused with  $R^{18,4}$ ;  $R^{18,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{19}$  is heteroaryl, which is unfused or fused with  $R^{19,4}$ ;  $R^{19,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{20}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with  $R^{20,4}$ ;  $R^{20,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{21}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{22}$ ,  $OR^{22}$ ,  $SR^{22}$ ,  $S(O)R^{22}$ ,  $SO_2R^{22}$ ,  $C(O)R^{22}$ ,  $CO(O)R^{22}$ ,  $OC(O)R^{22}$ ,  $OC(O)OR^{22}$ ,  $NH_2$ ,  $NHR^{22}$ ,  $N(R^{22})_2$ ,  $NHC(O)R^{22}$ ,  $NR^{22}C(O)R^{22}$ ,  $NHS(O)_2R^{22}$ ,  $NR^{22}S(O)_2R^{22}$ ,  $NHC(O)OR^{22}$ ,  $NR^{22}C(O)OR^{22}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{22}$ ,  $NHC(O)N(R^{22})_2$ ,  $NR^{22}C(O)NHR^{22}$ ,  $NR^{22}C(O)N(R^{22})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{22}$ ,  $C(O)N(R^{22})_2$ ,  $C(O)NHOH$ ,



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$C(O)NHOR^{22}$ ,  $C(O)NHSO_2R^{22}$ ,  $C(O)NR^{22}SO_2R^{22}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{22}$ ,  $SO_2N(R^{22})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{22}$ ,  $C(N)N(R^{22})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{22}$  is  $R^{23}$ ,  $R^{24}$  or  $R^{25}$ ;

$R^{23}$  is phenyl, which is unfused or fused with  $R^{23A}$ ;  $R^{23A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{24}$  is heteroarene, which is unfused or fused with  $R^{24A}$ ;  $R^{24A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{25}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{25A}$ ;  $R^{25A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$Z^1$  is  $R^{26}$  or  $R^{27}$ ;

$Z^2$  is  $R^{28}$ ,  $R^{29}$  or  $R^{30}$ ;

$Z^{1A}$  and  $Z^{2A}$  are both absent or are taken together to form  $CH_2$ ,  $CH_2CH_2$  or  $Z^{12A}$ ;

$Z^{12A}$  is  $C_2-C_6$ -alkylene having one or two  $CH_2$  moieties replaced by  $NH$ ,  $N(CH_3)$ ,  $S$ ,  $S(O)$  or  $SO_2$ ;

$L^1$  is a  $R^{37}$ ,  $OR^{37}$ ,  $SR^{37}$ ,  $S(O)R^{37}$ ,  $SO_2R^{37}$ ,  $C(O)R^{37}$ ,  $CO(O)R^{37}$ ,  $OC(O)R^{37}$ ,  $OC(O)OR^{37}$ ,  $NHR^{37}$ ,  $C(O)NH$ ,  $C(O)NR^{37}$ ,  $C(O)NHOR^{37}$ ,  $C(O)NHSO_2R^{37}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{37}$ ,  $C(N)NH$ ,  $C(N)NHR^{37}$ ;

$R^{26}$  is phenylene, which is unfused or fused with  $R^{26A}$ ;  $R^{26A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{27}$  is heteroaryl, which is unfused or fused with  $R^{27A}$ ;  $R^{27A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{28}$  is phenylene, which is unfused or fused with  $R^{28A}$ ;  $R^{28A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{29}$  is heteroaryl, which is unfused or fused with  $R^{29A}$ ;  $R^{29A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{30}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heterocycloalkenylene, each of which is unfused or fused with  $R^{30A}$ ;  $R^{30A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{37}$  is a bond or  $R^{37A}$ ;

$R^{37A}$  is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected  $R^{37B}$ ,  $OR^{37B}$ ,  $SR^{37B}$ ,  $S(O)R^{37B}$ ,  $SO_2R^{37B}$ ,  $C(O)R^{37B}$ ,  $CO(O)R^{37B}$ ,  $OC(O)R^{37B}$ ,  $OC(O)OR^{37B}$ ,  $NH_2$ ,  $NHR^{37B}$ ,  $N(R^{37B})_2$ ,  $NHC(O)R^{37B}$ ,  $NR^{37B}C(O)R^{37B}$ ,  $NHS(O)_2R^{37B}$ ,  $NR^{37B}S(O)_2R^{37B}$ ,  $NHC(O)OR^{37B}$ ,  $NR^{37B}C(O)OR^{37B}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{37B}$ ,  $NHC(O)N(R^{37B})_2$ ,  $NR^{37B}C(O)NHR^{37B}$ ,  $NR^{37B}C(O)N(R^{37B})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{37B}$ ,  $C(O)N(R^{37B})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{37B}$ ,  $C(O)NHSO_2R^{37B}$ ,  $C(O)NR^{37B}SO_2R^{37B}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{37B}$ ,  $SO_2N(R^{37B})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{37B}$ ,  $C(N)N(R^{37B})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  and  $I$  substituents;  $R^{37B}$  is alkyl, alkenyl, alkynyl, or  $R^{37C}$ ;

$R^{37C}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

$Z^3$  is  $R^{38}$ ,  $R^{39}$  or  $R^{40}$ ;

$R^{38}$  is phenyl, which is unfused or fused with  $R^{38A}$ ;  $R^{38A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{39}$  is heteroaryl, which is unfused or fused with  $R^{39A}$ ;  $R^{39A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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$R^{40}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{40A}$ ;  $R^{40A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by  $R^{26}$  and  $R^{27}$  are substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are absent) or further substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are present) with  $R^{41}$ ,  $OR^{41}$ ,  $SR^{41}$ ,  $S(O)R^{41}$ ,  $SO_2R^{41}$ ,  $C(O)R^{41}$ ,  $CO(O)R^{41}$ ,  $OC(O)R^{41}$ ,  $OC(O)OR^{41}$ ,  $NHR^{41}$ ,  $N(R^{41})_2$ ,  $NHC(O)R^{41}$ ,  $NR^{41}C(O)R^{41}$ ,  $NHS(O)_2R^{41}$ ,  $NR^{41}S(O)_2R^{41}$ ,  $NHC(O)OR^{41}$ ,  $NR^{41}C(O)OR^{41}$ ,  $NHC(O)NHR^{41}$ ,  $NHC(O)N(R^{41})_2$ ,  $NR^{41}C(O)NHR^{41}$ ,  $NR^{41}C(O)N(R^{41})_2$ ,  $C(O)NHR^{41}$ ,  $C(O)N(R^{41})_2$ ,  $C(O)NHOR^{41}$ ,  $C(O)NHSO_2R^{41}$ ,  $C(O)NR^{41}SO_2R^{41}$ ,  $SO_2NHR^{41}$ ,  $SO_2N(R^{41})_2$ ,  $C(N)NHR^{41}$ , or  $C(N)N(R^{41})_2$ ;

$R^{41}$  is heteroaryl, which is fused with  $R^{43A}$ ;  $R^{43A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused or fused with benzene, heteroarene or  $R^{43B}$ ;  $R^{43B}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by  $E^1$  and  $Y^1$  together,  $Y^1$  and  $B^1$  together,  $A^2$  and  $B^1$  together,  $A^2$  and  $D^1$  together,  $R^{1A}$ ,  $R^2$ ,  $R^{2A}$ ,  $R^3$ ,  $R^{3A}$ ,  $R^4$ ,  $R^{4A}$ ,  $R^6$ ,  $R^{6C}$ ,  $R^8$ ,  $R^{8A}$ ,  $R^9$ ,  $R^{9A}$ ,  $R^{10}$ ,  $R^{10A}$ ,  $R^{13}$ ,  $R^{13A}$ ,  $R^{14}$ ,  $R^{14A}$ ,  $R^{15}$ ,  $R^{15A}$ ,  $R^{18}$ ,  $R^{18A}$ ,  $R^{19}$ ,  $R^{19A}$ ,  $R^{20}$ ,  $R^{20A}$ ,  $R^{23}$ ,  $R^{23A}$ ,  $R^{24}$ ,  $R^{24A}$ ,  $R^{25}$ ,  $R^{25A}$ ,  $R^{26}$ ,  $R^{26A}$ ,  $R^{27}$ ,  $R^{27A}$ ,  $R^{28}$ ,  $R^{28A}$ ,  $R^{29}$ ,  $R^{29A}$ ,  $R^{30}$ ,  $R^{30A}$ ,  $R^{37B}$ ,  $R^{38}$ ,  $R^{38A}$ ,  $R^{39}$ ,  $R^{39A}$ ,  $R^{40}$ , and  $R^{40A}$  are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SR^{57}$ ,  $S(O)R^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $OC(O)R^{57}$ ,  $OC(O)OR^{57}$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NR^{57}C(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $NR^{57}S(O)_2R^{57}$ ,  $NHC(O)OR^{57}$ ,  $NR^{57}C(O)OR^{57}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{57}$ ,  $NHC(O)N(R^{57})_2$ ,  $NR^{57}C(O)NHR^{57}$ ,  $NR^{57}C(O)N(R^{57})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{57}$ ,  $C(O)N(R^{57})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{57}$ ,  $C(O)NHSO_2R^{57}$ ,  $C(O)NR^{57}SO_2R^{57}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{57}$ ,  $SO_2N(R^{57})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{57}$ ,  $C(N)N(R^{57})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl, which is unfused or fused with  $R^{58A}$ ;  $R^{58A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{59}$  is heteroaryl, which is unfused or fused with  $R^{59A}$ ;  $R^{59A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{60}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{60A}$ ;  $R^{60A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{61}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $SR^{62}$ ,  $S(O)R^{62}$ ,  $SO_2R^{62}$ ,  $C(O)R^{62}$ ,  $CO(O)R^{62}$ ,  $OC(O)R^{62}$ ,  $OC(O)OR^{62}$ ,  $NH_2$ ,  $NHR^{62}$ ,  $N(R^{62})_2$ ,  $NHC(O)R^{62}$ ,  $NR^{62}C(O)R^{62}$ ,  $NHS(O)_2R^{62}$ ,  $NR^{62}S(O)_2R^{62}$ ,  $NHC(O)OR^{62}$ ,  $NR^{62}C(O)OR^{62}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{62}$ ,  $NHC(O)N(R^{62})_2$ ,  $NR^{62}C(O)NHR^{62}$ ,  $NR^{62}C(O)N(R^{62})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{62}$ ,  $C(O)N(R^{62})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{62}$ ,  $C(O)NHSO_2R^{62}$ ,  $C(O)NR^{62}SO_2R^{62}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{62}$ ,  $SO_2N(R^{62})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{62}$ ,  $C(N)N(R^{62})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

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$R^{62}$  is  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$  or  $R^{66}$ ;

$R^{63}$  is phenyl, which is unfused or fused with  $R^{63A}$ ;  $R^{63A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{64}$  is heteroaryl, which is unfused or fused with  $R^{64A}$ ;  $R^{64A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{65}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with  $R^{65A}$ ;  $R^{65A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{66}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{67}$ ,  $OR^{67}$ ,  $SR^{67}$ ,  $S(O)R^{67}$ ,  $SO_2R^{67}$ ,  $C(O)R^{67}$ ,  $CO(O)R^{67}$ ,  $OC(O)R^{67}$ ,  $OC(O)OR^{67}$ ,  $NH_2$ ,  $NHR^{67}$ ,  $N(R^{67})_2$ ,  $NHC(O)R^{67}$ ,  $NR^{67}C(O)R^{67}$ ,  $NHS(O)_2R^{67}$ ,  $NR^{67}S(O)_2R^{67}$ ,  $NHC(O)OR^{67}$ ,  $NR^{67}C(O)OR^{67}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{67}$ ,  $NHC(O)N(R^{67})_2$ ,  $NR^{67}C(O)NHR^{67}$ ,  $NR^{67}C(O)N(R^{67})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{67}$ ,  $C(O)N(R^{67})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{67}$ ,  $C(O)NHSO_2R^{67}$ ,  $C(O)NR^{67}SO_2R^{67}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{67}$ ,  $SO_2N(R^{67})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{67}$ ,  $C(N)N(R^{67})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$  substituents;

$R^{67}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$ ,  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$ , and  $R^{67}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $OR^{68}$ ,  $SR^{68}$ ,  $S(O)R^{68}$ ,  $SO_2R^{68}$ ,  $C(O)R^{68}$ ,  $CO(O)R^{68}$ ,  $OC(O)R^{68}$ ,  $OC(O)OR^{68}$ ,  $NH_2$ ,  $NHR^{68}$ ,  $N(R^{68})_2$ ,  $NHC(O)R^{68}$ ,  $NR^{68}C(O)R^{68}$ ,  $NHS(O)_2R^{68}$ ,  $NR^{68}S(O)_2R^{68}$ ,  $NHC(O)OR^{68}$ ,  $NR^{68}C(O)OR^{68}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{68}$ ,  $NHC(O)N(R^{68})_2$ ,  $NR^{68}C(O)NHR^{68}$ ,  $NR^{68}C(O)N(R^{68})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{68}$ ,  $C(O)N(R^{68})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{68}$ ,  $C(O)NHSO_2R^{68}$ ,  $C(O)NR^{68}SO_2R^{68}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{68}$ ,  $SO_2N(R^{68})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{68}$ ,  $C(N)N(R^{68})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{68}$  is  $R^{69}$ ,  $R^{70}$ ,  $R^{71}$  or  $R^{72}$ ;

$R^{69}$  is phenyl, which is unfused or fused with  $R^{69A}$ ;  $R^{69A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{70}$  is heteroaryl, which is unfused or fused with  $R^{70A}$ ;  $R^{70A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{71}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{71A}$ ;  $R^{71A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{72}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{73}$ ,  $OR^{73}$ ,  $SR^{73}$ ,  $S(O)R^{73}$ ,  $SO_2R^{73}$ ,  $C(O)R^{73}$ ,  $CO(O)R^{73}$ ,  $OC(O)R^{73}$ ,  $OC(O)OR^{73}$ ,  $NH_2$ ,  $NHR^{73}$ ,  $N(R^{73})_2$ ,  $NHC(O)R^{73}$ ,  $NR^{73}C(O)R^{73}$ ,  $NHS(O)_2R^{73}$ ,  $NR^{73}S(O)_2R^{73}$ ,  $NHC(O)OR^{73}$ ,  $NR^{73}C(O)OR^{73}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{73}$ ,  $NHC(O)N(R^{73})_2$ ,  $NR^{73}C(O)NHR^{73}$ ,  $NR^{73}C(O)N(R^{73})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{73}$ ,  $C(O)N(R^{73})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{73}$ ,  $C(O)NHSO_2R^{73}$ ,  $C(O)NR^{73}SO_2R^{73}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{73}$ ,  $SO_2N(R^{73})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{73}$ ,  $C(N)N(R^{73})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

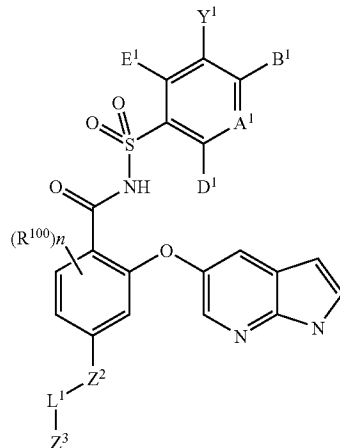
$R^{73}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

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wherein the moieties represented by  $R^{69}$ ,  $R^{70}$ , and  $R^{71}$  are unsubstituted or substituted with one or two or three or four of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $C(O)NHOH$ ,  $SO_2NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ .

Another embodiment of this invention pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (II)

(II)



or a therapeutically acceptable salt thereof, wherein

$R^{100}$  is as described for substituents on  $R^{26}$ ;

$n$  is 0, 1, 2, or 3;

$A^1$  is  $N$  or  $C(A^2)$ ;

$A^2$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ;

$B^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ;

$D^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,

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$C(NH)N(R^1)_2NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

E<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, N(CH<sub>3</sub>)SO<sub>2</sub>NHR<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; and

Y<sup>1</sup> is H, CN,  $NO_2$ , C(O)OH, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, C(O)R<sup>17</sup>, C(O)OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, NH<sub>2</sub>, NHR<sup>17</sup>, N(R<sup>17</sup>)<sub>2</sub>, NHC(O)R<sup>17</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>17</sup>, C(O)N(R<sup>17</sup>)<sub>2</sub>, NHC(O)R<sup>17</sup> or NHC(O)R<sup>17</sup>; or

E<sup>1</sup> and Y<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, B<sup>1</sup>, and D<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, N(CH<sub>3</sub>)SO<sub>2</sub>NHR<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, N(CH<sub>3</sub>)SO<sub>2</sub>NHR<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

A<sup>2</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, N(CH<sub>3</sub>)SO<sub>2</sub>NHR<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

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A<sup>2</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

B<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, N(CH<sub>3</sub>)SO<sub>2</sub>NHR<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

R<sup>1</sup> is R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup>;

R<sup>1,4</sup> is cycloalkyl, cycloalkenyl or cycloalkynyl;

R<sup>2</sup> is phenyl, which is unfused or fused with R<sup>2,4</sup>; R<sup>2,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>3</sup> is heteroaryl, which is unfused or fused with R<sup>3,4</sup>; R<sup>3,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>4,4</sup>; R<sup>4,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>5</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>6</sup>, NC(R<sup>6,4</sup>)(R<sup>6,5</sup>), R<sup>7</sup>, OR<sup>7</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, C(O)R<sup>7</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>7</sup>, C(O)N(R<sup>7</sup>)<sub>2</sub>, NHC(O)R<sup>7</sup>, NR<sup>7</sup>C(O)R<sup>7</sup>, NH<sub>2</sub>SO<sub>2</sub>R<sup>7</sup>, NHC(O)OR<sup>7</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>7</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>7</sup>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NHR<sup>7</sup>, OH, (O), C(O)OH,  $N_3$ , CN, NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>6</sup> is C<sub>2</sub>-C<sub>5</sub>-spiroalkyl, each of which is unsubstituted or substituted with OH, (O),  $N_3$ , CN, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, NH<sub>2</sub>, NH(CH<sub>3</sub>) or N(CH<sub>3</sub>)<sub>2</sub>;

R<sup>6,4</sup> and R<sup>6,5</sup> are independently selected alkyl or, together with the N to which they are attached, R<sup>6,6</sup>;

R<sup>6,6</sup> is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH<sub>2</sub> moiety unreplaced or replaced with O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup>;

R<sup>8</sup> is phenyl, which is unfused or fused with R<sup>8,4</sup>; R<sup>8,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>9</sup> is heteroaryl, which is unfused or fused with R<sup>9,4</sup>; R<sup>9,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>10,4</sup>; R<sup>10,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>11</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup>, SR<sup>12</sup>, S(O)R<sup>12</sup>, SO<sub>2</sub>R<sup>12</sup>, C(O)R<sup>12</sup>, CO(O)R<sup>12</sup>, OC(O)R<sup>12</sup>, OC(O)OR<sup>12</sup>, NH<sub>2</sub>, NHR<sup>12</sup>, N(R<sup>12</sup>)<sub>2</sub>, NHC(O)R<sup>12</sup>, NR<sup>12</sup>C(O)R<sup>12</sup>, NH<sub>2</sub>SO<sub>2</sub>R<sup>12</sup>, NHC(O)OR<sup>12</sup>, NR<sup>12</sup>C(O)OR<sup>12</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>12</sup>, NHC(O)N(R<sup>12</sup>)<sub>2</sub>, NR<sup>12</sup>C(O)NHR<sup>12</sup>, NR<sup>12</sup>C(O)N(R<sup>12</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>12</sup>, SO<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>12</sup>, NR<sup>12</sup>SO<sub>2</sub>R<sup>12</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>12</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>, C(O)NHNOR<sup>12</sup>, C(O)NHSO<sub>2</sub>R<sup>12</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>12</sup>, C(NH)N(R<sup>12</sup>)<sub>2</sub>, N(CH<sub>3</sub>)SO<sub>2</sub>NHR<sup>12</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>12</sup>, F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or



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NH<sub>2</sub>, C(N)NHR<sup>12</sup>, C(N)N(R<sup>12</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>12</sup> is R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> or R<sup>16</sup>;

R<sup>13</sup> is phenyl, which is unfused or fused with R<sup>13A</sup>; R<sup>13A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>14</sup> is heteroaryl, which is unfused or fused with R<sup>14A</sup>; R<sup>14A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>15</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R<sup>15A</sup>; R<sup>15A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>16</sup> is alkyl, alkenyl or alkynyl;

R<sup>17</sup> is R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> or R<sup>21</sup>;

R<sup>18</sup> is phenyl, which is unfused or fused with R<sup>18A</sup>; R<sup>18A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>19</sup> is heteroaryl, which is unfused or fused with R<sup>19A</sup>; R<sup>19A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>20</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R<sup>20A</sup>; R<sup>20A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>21</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, OR<sup>22</sup>, SR<sup>22</sup>, S(O)R<sup>22</sup>, SO<sub>2</sub>R<sup>22</sup>, C(O)R<sup>22</sup>, CO(O)R<sup>22</sup>, OC(O)R<sup>22</sup>, OC(O)OR<sup>22</sup>, NH<sub>2</sub>, NHR<sup>22</sup>, N(R<sup>22</sup>)<sub>2</sub>, NHC(O)R<sup>22</sup>, NR<sup>22</sup>C(O)R<sup>22</sup>, NHS(O)<sub>2</sub>R<sup>22</sup>, NR<sup>22</sup>S(O)<sub>2</sub>R<sup>22</sup>, NHC(O)OR<sup>22</sup>, NR<sup>22</sup>C(O)OR<sup>22</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>22</sup>, NHC(O)N(R<sup>22</sup>)<sub>2</sub>, NR<sup>22</sup>C(O)NHR<sup>22</sup>, NR<sup>22</sup>C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>22</sup>, C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>22</sup>, C(O)NHSO<sub>2</sub>R<sup>22</sup>, C(O)NR<sup>22</sup>SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>22</sup>, SO<sub>2</sub>N(R<sup>22</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>22</sup>, C(N)N(R<sup>22</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>23</sup>, R<sup>24</sup> or R<sup>25</sup>;

R<sup>23</sup> is phenyl, which is unfused or fused with R<sup>23A</sup>; R<sup>23A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>24</sup> is heteroarene, which is unfused or fused with R<sup>24A</sup>; R<sup>24A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>25</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>25A</sup>; R<sup>25A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z<sup>2</sup> is R<sup>28</sup>, R<sup>29</sup> or R<sup>30</sup>;

L<sup>1</sup> is a R<sup>37</sup>, OR<sup>37</sup>, SR<sup>37</sup>, S(O)R<sup>37</sup>, SO<sub>2</sub>R<sup>37</sup>, C(O)R<sup>37</sup>, CO(O)R<sup>37</sup>, OC(O)R<sup>37</sup>, OC(O)OR<sup>37</sup>, NHR<sup>37</sup>, C(O)NH, C(O)NR<sup>37</sup>, C(O)NHOR<sup>37</sup>, C(O)NHSO<sub>2</sub>R<sup>37</sup>, SO<sub>2</sub>NH, SO<sub>2</sub>NHR<sup>37</sup>, C(N)NH, C(N)NHR<sup>37</sup>;

R<sup>28</sup> is phenylene, which is unfused or fused with R<sup>28A</sup>; R<sup>28A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>29</sup> is heteroarylene, which is unfused or fused with R<sup>29A</sup>; R<sup>29A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>30</sup> is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R<sup>30A</sup>; R<sup>30A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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R<sup>37</sup> is a bond or R<sup>37A</sup>;

R<sup>37A</sup> is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R<sup>37B</sup>, OR<sup>37B</sup>, SR<sup>37B</sup>, S(O)R<sup>37B</sup>, SO<sub>2</sub>R<sup>37B</sup>, C(O)R<sup>37B</sup>, CO(O)R<sup>37B</sup>, OC(O)R<sup>37B</sup>, OC(O)OR<sup>37B</sup>, NH<sub>2</sub>, NHR<sup>37B</sup>, N(R<sup>37B</sup>)<sub>2</sub>, NHC(O)R<sup>37B</sup>, NR<sup>37B</sup>C(O)R<sup>37B</sup>, NHS(O)<sub>2</sub>R<sup>37B</sup>, NR<sup>37B</sup>S(O)<sub>2</sub>R<sup>37B</sup>, NHC(O)OR<sup>37B</sup>, NR<sup>37B</sup>C(O)OR<sup>37B</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>37B</sup>, NHC(O)N(R<sup>37B</sup>)<sub>2</sub>, NR<sup>37B</sup>C(O)NHR<sup>37B</sup>, NR<sup>37B</sup>C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>37B</sup>, C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>37B</sup>, C(O)NHSO<sub>2</sub>R<sup>37B</sup>, C(O)NR<sup>37B</sup>SO<sub>2</sub>R<sup>37B</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>37B</sup>, SO<sub>2</sub>N(R<sup>37B</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>37B</sup>, C(N)N(R<sup>37B</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br and I substituents;

R<sup>37B</sup> is alkyl, alkenyl, alkynyl, or R<sup>37C</sup>;

R<sup>37C</sup> is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

Z<sup>3</sup> is R<sup>38</sup>, R<sup>39</sup> or R<sup>40</sup>;

R<sup>38</sup> is phenyl, which is unfused or fused with R<sup>38A</sup>; R<sup>38A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>39</sup> is heteroaryl, which is unfused or fused with R<sup>39A</sup>; R<sup>39A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>40</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>40A</sup>; R<sup>40A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by E<sup>1</sup> and Y<sup>1</sup> together, Y<sup>1</sup> and B<sup>1</sup> together, A<sup>2</sup> and B<sup>1</sup> together, A<sup>2</sup> and D<sup>1</sup> together, R<sup>1A</sup>, R<sup>2</sup>, R<sup>2A</sup>, R<sup>3</sup>, R<sup>3A</sup>, R<sup>4</sup>, R<sup>4A</sup>, R<sup>6</sup>, R<sup>6C</sup>, R<sup>8</sup>, R<sup>8A</sup>, R<sup>9</sup>, R<sup>9A</sup>, R<sup>10</sup>, R<sup>10A</sup>, R<sup>13</sup>, R<sup>13A</sup>, R<sup>14</sup>, R<sup>14A</sup>, R<sup>15</sup>, R<sup>15A</sup>, R<sup>18</sup>, R<sup>18A</sup>, R<sup>19</sup>, R<sup>19A</sup>, R<sup>20</sup>, R<sup>20A</sup>, R<sup>23</sup>, R<sup>23A</sup>, R<sup>24</sup>, R<sup>24A</sup>, R<sup>25</sup>, R<sup>25A</sup>, R<sup>26</sup>, R<sup>26A</sup>, R<sup>27</sup>, R<sup>27A</sup>, R<sup>28</sup>, R<sup>28A</sup>, R<sup>29</sup>, R<sup>29A</sup>, R<sup>30</sup>, R<sup>30A</sup>, R<sup>37B</sup>, R<sup>38</sup>, R<sup>38A</sup>, R<sup>39</sup>, R<sup>39A</sup>, R<sup>40</sup>, and R<sup>40A</sup> are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SR<sup>57</sup>, S(O)R<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, OC(O)R<sup>57</sup>, OC(O)OR<sup>57</sup>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NR<sup>57</sup>C(O)R<sup>57</sup>, NHS(O)<sub>2</sub>R<sup>57</sup>, NR<sup>57</sup>S(O)<sub>2</sub>R<sup>57</sup>, NHC(O)OR<sup>57</sup>, NR<sup>57</sup>C(O)OR<sup>57</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>57</sup>, NHC(O)N(R<sup>57</sup>)<sub>2</sub>, NR<sup>57</sup>C(O)NHR<sup>57</sup>, NR<sup>57</sup>C(O)N(R<sup>57</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>57</sup>, C(O)NHSO<sub>2</sub>R<sup>57</sup>, C(O)NR<sup>57</sup>SO<sub>2</sub>R<sup>57</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>57</sup>, SO<sub>2</sub>N(R<sup>57</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>57</sup>, C(N)N(R<sup>57</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>57A</sup> is spiroalkyl or heterospiroalkyl;

R<sup>57</sup> is R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup> or R<sup>61</sup>;

R<sup>58</sup> is phenyl, which is unfused or fused with R<sup>58A</sup>; R<sup>58A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>59</sup> is heteroaryl, which is unfused or fused with R<sup>59A</sup>; R<sup>59A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>60</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>60A</sup>; R<sup>60A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>61</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, SR<sup>62</sup>, S(O)R<sup>62</sup>, SO<sub>2</sub>R<sup>62</sup>, C(O)R<sup>62</sup>, CO(O)R<sup>62</sup>, OC(O)R<sup>62</sup>, OC(O)OR<sup>62</sup>, NH<sub>2</sub>, NHR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, NHC(O)R<sup>62</sup>, NR<sup>62</sup>C(O)R<sup>62</sup>, NHS(O)<sub>2</sub>R<sup>62</sup>, NR<sup>62</sup>S(O)<sub>2</sub>R<sup>62</sup>, NHC(O)OR<sup>62</sup>, NR<sup>62</sup>C(O)OR<sup>62</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>62</sup>, NHC(O)N(R<sup>62</sup>)<sub>2</sub>, NR<sup>62</sup>C(O)NHR<sup>62</sup>, NR<sup>62</sup>C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>62</sup>, C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NHOH,



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C(O)NHOR<sup>62</sup>, C(O)NHSO<sub>2</sub>R<sup>62</sup>, C(O)NR<sup>62</sup>SO<sub>2</sub>R<sup>62</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>62</sup>, SO<sub>2</sub>N(R<sup>62</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>62</sup>, C(N)N(R<sup>62</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>62</sup> is R<sup>63</sup>, R<sup>64</sup>, R<sup>65</sup> or R<sup>66</sup>;

R<sup>63</sup> is phenyl, which is unfused or fused with R<sup>63A</sup>; R<sup>63A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>64</sup> is heteroaryl, which is unfused or fused with R<sup>64A</sup>; R<sup>64A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>65</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>65A</sup>; R<sup>65A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>66</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>67</sup>, OR<sup>67</sup>, SR<sup>67</sup>, S(O)R<sup>67</sup>, SO<sub>2</sub>R<sup>67</sup>, C(O)R<sup>67</sup>, CO(O)R<sup>67</sup>, OC(O)R<sup>67</sup>, OC(O)OR<sup>67</sup>, NH<sub>2</sub>, NHR<sup>67</sup>, N(R<sup>67</sup>)<sub>2</sub>, NHC(O)R<sup>67</sup>, NR<sup>67</sup>C(O)R<sup>67</sup>, NHS(O)<sub>2</sub>R<sup>67</sup>, NR<sup>67</sup>S(O)<sub>2</sub>R<sup>67</sup>, NHC(O)OR<sup>67</sup>, NR<sup>67</sup>C(O)OR<sup>67</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>67</sup>, NHC(O)N(R<sup>67</sup>)<sub>2</sub>, NR<sup>67</sup>C(O)NHR<sup>67</sup>, NR<sup>67</sup>C(O)N(R<sup>67</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>67</sup>, C(O)N(R<sup>67</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>67</sup>, C(O)NHSO<sub>2</sub>R<sup>67</sup>, C(O)NR<sup>67</sup>SO<sub>2</sub>R<sup>67</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>67</sup>, SO<sub>2</sub>N(R<sup>67</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>67</sup>, C(N)N(R<sup>67</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I substituents;

R<sup>67</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup>, R<sup>63</sup>, R<sup>64</sup>, R<sup>65</sup>, and R<sup>67</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, OR<sup>68</sup>, SR<sup>68</sup>, S(O)R<sup>68</sup>, SO<sub>2</sub>R<sup>68</sup>, C(O)R<sup>68</sup>, CO(O)R<sup>68</sup>, OC(O)R<sup>68</sup>, OC(O)OR<sup>68</sup>, NH<sub>2</sub>, NHR<sup>68</sup>, N(R<sup>68</sup>)<sub>2</sub>, NHC(O)R<sup>68</sup>, NR<sup>68</sup>C(O)R<sup>68</sup>, NHS(O)<sub>2</sub>R<sup>68</sup>, NR<sup>68</sup>S(O)<sub>2</sub>R<sup>68</sup>, NHC(O)OR<sup>68</sup>, NR<sup>68</sup>C(O)OR<sup>68</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>68</sup>, NHC(O)N(R<sup>68</sup>)<sub>2</sub>, NR<sup>68</sup>C(O)NHR<sup>68</sup>, NR<sup>68</sup>C(O)N(R<sup>68</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>68</sup>, C(O)N(R<sup>68</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>68</sup>, C(O)NHSO<sub>2</sub>R<sup>68</sup>, C(O)NR<sup>68</sup>SO<sub>2</sub>R<sup>68</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>68</sup>, SO<sub>2</sub>N(R<sup>68</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>68</sup>, C(N)N(R<sup>68</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>68</sup> is R<sup>69</sup>, R<sup>70</sup>, R<sup>71</sup> or R<sup>72</sup>;

R<sup>69</sup> is phenyl, which is unfused or fused with R<sup>69A</sup>; R<sup>69A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>70</sup> is heteroaryl, which is unfused or fused with R<sup>70A</sup>; R<sup>70A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>71</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>71A</sup>; R<sup>71A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>72</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>73</sup>, OR<sup>73</sup>, SR<sup>73</sup>, S(O)R<sup>73</sup>, SO<sub>2</sub>R<sup>73</sup>, C(O)R<sup>73</sup>, CO(O)R<sup>73</sup>, OC(O)R<sup>73</sup>, OC(O)OR<sup>73</sup>, NH<sub>2</sub>, NHR<sup>73</sup>, N(R<sup>73</sup>)<sub>2</sub>, NHC(O)R<sup>73</sup>, NR<sup>73</sup>C(O)R<sup>73</sup>, NHS(O)<sub>2</sub>R<sup>73</sup>, NR<sup>73</sup>S(O)<sub>2</sub>R<sup>73</sup>, NHC(O)OR<sup>73</sup>, NR<sup>73</sup>C(O)OR<sup>73</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>73</sup>, NHC(O)N(R<sup>73</sup>)<sub>2</sub>, NR<sup>73</sup>C(O)NHR<sup>73</sup>, NR<sup>73</sup>C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>73</sup>, C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>73</sup>, C(O)NHSO<sub>2</sub>R<sup>73</sup>, C(O)NR<sup>73</sup>SO<sub>2</sub>R<sup>73</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>73</sup>, SO<sub>2</sub>N(R<sup>73</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>73</sup>, C(N)N(R<sup>73</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

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NH<sub>2</sub>, C(N)NHR<sup>73</sup>, C(N)N(R<sup>73</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>73</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R<sup>69</sup>, R<sup>70</sup>, and R<sup>71</sup> are unsubstituted or substituted with one or two or three or four of independently selected NH<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H, and G<sup>1</sup> is H.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; G<sup>1</sup> is H, and B<sup>1</sup> is NHR<sup>1</sup>.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; G<sup>1</sup> is H, B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; G<sup>1</sup> is H, B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; G<sup>1</sup> is H, B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-({3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-({4-[(1,4-dioxan-2-yl-methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{(tetrahydro-2H-pyran-4-ylmethyl)amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl]benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl]benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)amino]-3-(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5-[(4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;

N-[(5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2,2-dimethyltetrahydro-

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2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({4-[(1-acetyl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-N-({[4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl)amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[1-(methylpiperidin-4-yl)methyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-([4-({[4-methoxycyclohexyl]methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-([4-({[4-methoxycyclohexyl]methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 tert-butyl 3-([4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxymethyl)morpholine-4-carboxylate;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[1-(methylsulfonyl)piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([4-chloro-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-





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Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-{{4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}amino}sulfonyl)-2-nitrophenoxymethyl]-4-fluoropiperidine-1-carboxylate;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(3-nitro-4-{{4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl}cyclohexyl}amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{4-{{1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(3-nitro-4-{{(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(3-nitro-4-{{(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{4-{{4-(2-methoxyethyl)morpholin-2-yl)methyl}amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(1-cyclobutylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{3-nitro-4-{{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{4-{{1-(methylsulfonyl)piperidin-3-yl)methyl}amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(1-acetyl)piperidin-3-yl]methyl}amino}-3-nitrophenyl)sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{4-{{1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-{{4-{{1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-{{(3S)-2-oxopiperidin-3-yl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({4-({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}methyl)amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-{{(1-oxetan-3-ylazetidin-3-yl)methyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-{{(1-oxetan-3-ylpiperidin-4-yl)methyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-{{(1-cyclopropylpiperidin-4-yl)methyl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-({[(4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-({[(4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-{{(4-fluoro-1-oxetan-3-ylpiperidin-4-yl)methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-{{(4-(2-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-{{(4-cyclobutylmorpholin-3-yl)methyl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-{{(4-tetrahydrofuran-3-ylmorpholin-3-yl)methyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-{{(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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ethyl)ethyl]piperidin-4-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({3-(trifluoromethoxy)benzyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({4-(difluoromethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-([4-({4-(acetylaminocyclohexyl)amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({3-(difluoromethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[cis-3-morpholin-4-ylcyclopentyl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(2-morpholin-4-ylethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

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droxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(2-methoxyethoxy)ethyl]morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

(2-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino)methyl)morpholin-4-yl)acetic acid;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-

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pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

ethyl 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-[(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenylamino]piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro- $\lambda^6$ -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-1,3-difluoropropan-



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2-yl)morpholin-2-yl)methyl}amino-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[3-nitro-4-[[1-(oxetan-3-yl)azetidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((2R)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl}amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((2S)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl}amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-(cyanomethyl)pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 N-((5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 10 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-((5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 20 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-((4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)-3-(trifluoromethyl)phenyl)sulfonyl)benzamide;  
 25 N-[(5-chloro-6-[[1-(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(trans-4-cyanocyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 35 4-(4-{[5-chloro-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 45 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-(3-furylmethoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 50 N-[(5-chloro-6-[[1-(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 55 N-[(5-chloro-6-[[1-(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 60 N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 65 N-((3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-

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dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-([1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-([1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropylamino)propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(methoxyacetyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)benzamide;  
 N-([5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-[(4-fluorotetrahy-

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dro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([trans-4-(morpholin-4-yl)cyclohexyl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(2,2,2-trifluoroethyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(oxetan-3-yl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(oxetan-3-yl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([2S]-4-cyclopropylmorpholin-2-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-

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pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 methyl 2-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]methyl]morpholine-4-carboxylate;

10 2-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-(4-{[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-(4-{[3-(cyclobutyl(cyclopropyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([trans-4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

40 N-([3-chloro-4-([4-fluorotetrahydro-2H-pyran-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-([2-(2R)-4-cyclopropylmorpholin-2-yl]methyl)amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

45 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-([2S)-4-cyclopropylmorpholin-2-yl]methyl)amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

50 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[[5-chloro-6-([4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy]pyridin-3-yl]sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-[[4-([4-(cyclopropylmorpholin-2-yl)methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

65 N-([3-chloro-4-([4-(cyclopropylmorpholin-2-yl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimeth-

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ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-([4-(cyclopropylmorpholin-2-yl)methyl]amino)phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 2-[[2-chloro-4-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

10 (2S)-2-[[3-chloro-5-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl]oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

15 N-[(5-chloro-6-([4-(cyclopropylmorpholin-2-yl)methyl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 2-[[3-chloro-5-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([trans-4-hydroxy-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([cis-4-hydroxy-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

35 N-[(5-chloro-6-([1R,2R,4R,5R]-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-([2-cyanoethyl](cyclopropyl)amino)cyclohexyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

40 N-([5-chloro-6-([trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

50 N-[(5-chloro-6-([1R,2S,4R,5R]-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

55 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

60 N-[(5-chloro-6-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

65 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl]amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl]methoxy}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl)amino}methyl pivalate;

{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl)amino}methyl butyrate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl}benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl)-2-nitrophenyl)morpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(methoxymethyl)cyclohexyl]methyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof. Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]

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methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-[(5-chloro-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino]propyl]amino}-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-py-

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ran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino]propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(5-chloro-6-[(1-cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino]propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino]propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(1,4-dioxan-2-yl)methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-

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pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to a composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of a compound of Formula (I) or Formula (II).

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or Formula (II).

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of Formula (I) or Formula (II) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

#### DETAILED DESCRIPTION OF THE INVENTION

Variable moieties herein are represented by identifiers (capital letters with numerical and/or alphabetical superscripts) and may be specifically embodied.

It is meant to be understood that proper valences are maintained for all moieties and combinations thereof, that monovalent moieties having more than one atom are drawn from left to right and are attached through their left ends, and that divalent moieties are also drawn from left to right.

It is also meant to be understood that a specific embodiment of a variable moiety herein may be the same or different as another specific embodiment having the same identifier.

The term "alkenyl" as used herein, means a straight or branched hydrocarbon chain containing from 2 to 10 carbons and containing at least one carbon-carbon double bond. The term "C<sub>x</sub>-C<sub>y</sub> alkenyl" means a straight or branched hydrocarbon chain containing at least one carbon-carbon double bond containing x to y carbon atoms. The term "C<sub>3</sub>-C<sub>6</sub> alkenyl" means an alkenyl group containing 3-6 carbon atoms. Representative examples of alkenyl include, but are not limited to, buta-2,3-dienyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.



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The term “alkenylene” means a divalent group derived from a straight or branched chain hydrocarbon of 2 to 4 carbon atoms and contains at least one carbon-carbon double bond. The term “C<sub>x</sub>-C<sub>y</sub> alkenylene” means a divalent group derived from a straight or branched hydrocarbon chain containing at least one carbon-carbon double bond and containing x to y carbon atoms. Representative examples of alkenylene include, but are not limited to, —CH=CH— and —CH<sub>2</sub>CH=CH—.

The term “alkyl” as used herein, means a straight or branched, saturated hydrocarbon chain containing from 1 to 10 carbon atoms. The term “C<sub>x</sub>-C<sub>y</sub> alkyl” means a straight or branched chain, saturated hydrocarbon containing x to y carbon atoms. For example “C<sub>1</sub>-C<sub>6</sub> alkyl” means a straight or branched chain, saturated hydrocarbon containing 2 to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term “alkylene” means a divalent group derived from a straight or branched, saturated hydrocarbon chain of 1 to 10 carbon atoms, for example, of 1 to 4 carbon atoms. The term “C<sub>x</sub>-C<sub>y</sub> alkylene” means a divalent group derived from a straight or branched chain, saturated hydrocarbon containing x to y carbon atoms. For example “C<sub>2</sub>-C<sub>6</sub> alkylene” means a straight or branched chain, saturated hydrocarbon containing 2 to 6 carbon atoms. Representative examples of alkylene include, but are not limited to, —CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>—, and —CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>—.

The term “alkynyl” as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond.

The term “C<sub>x</sub>-C<sub>y</sub> alkynyl” means a straight or branched chain hydrocarbon group containing from x to y carbon atoms. For example “C<sub>3</sub>-C<sub>6</sub> alkynyl” means a straight or branched chain hydrocarbon group containing from 3 to 6 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited to, acetylenyl, 1-propynyl, 2-propynyl, 3-butylnyl, 2-pentylnyl, and 1-butylnyl.

The term “alkynylene,” as used herein, means a divalent radical derived from a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond.

The term “aryl” as used herein, means phenyl.

The term “cyclic moiety,” as used herein, means benzene, phenyl, phenylene, cycloalkane, cycloalkyl, cycloalkylene, cycloalkene, cycloalkenyl, cycloalkenylene, cycloalkyne, cycloalkynyl, cycloalkynylene, heteroarene, heteroaryl, heterocycloalkane, heterocycloalkyl, heterocycloalkene, heterocycloalkenyl and spiroalkyl.

The term “cycloalkylene” or “cycloalkyl” or “cycloalkane” as used herein, means a monocyclic or bridged hydrocarbon ring system. The monocyclic cycloalkyl is a carbocyclic ring system containing three to ten carbon atoms, zero heteroatoms and zero double bonds. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The monocyclic ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. Representative examples of such bridged cycloalkyl ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo

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[3.3.1]nonane, bicyclo[4.2.1]nonane, tricyclo[3.3.1.0<sup>3,7</sup>]nonane (octahydro-2,5-methanopentalene or noradamantane), and tricyclo[3.3.1.1<sup>3,7</sup>]decane (adamantane). The monocyclic and bridged cycloalkyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring system.

The term “cycloalkenylene,” or “cycloalkenyl” or “cycloalkene” as used herein, means a monocyclic or a bridged hydrocarbon ring system. The monocyclic cycloalkenyl has four to ten carbon atoms and zero heteroatoms. The four-membered ring systems have one double bond, the five- or six-membered ring systems have one or two double bonds, the seven- or eight-membered ring systems have one, two, or three double bonds, and the nine- or ten-membered rings have one, two, three, or four double bonds. Representative examples of monocyclic cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. The monocyclic cycloalkenyl ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. Representative examples of the bridged cycloalkenyl groups include, but are not limited to, 4,5,6,7-tetrahydro-3aH-indene, octahydronaphthalenyl, and 1,6-dihydro-pentalene. The monocyclic and bridged cycloalkenyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems.

The term “cycloalkyne,” or “cycloalkynyl,” or “cycloalkynylene,” as used herein, means a monocyclic or a bridged hydrocarbon ring system. The monocyclic cycloalkynyl has eight or more carbon atoms, zero heteroatoms, and one or more triple bonds. The monocyclic cycloalkynyl ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. The monocyclic and bridged cycloalkynyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems.

The term “heteroarene,” or “heteroaryl,” or “heteroarylene,” as used herein, means a five-membered or six-membered aromatic ring having at least one carbon atom and one or more than one independently selected nitrogen, oxygen or sulfur atom. The heteroarenes of this invention are connected through any adjacent atoms in the ring, provided that proper valences are maintained. Representative examples of heteroaryl include, but are not limited to, furanyl (including, but not limited thereto, furan-2-yl), imidazolyl (including, but not limited thereto, 1H-imidazol-1-yl), isoxazolyl, isothiazolyl, oxadiazolyl, 1,3-oxazolyl, pyridinyl (e.g. pyridin-4-yl, pyridin-2-yl, pyridin-3-yl), pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, 1,3-thiazolyl, thienyl (including, but not limited thereto, thien-2-yl, thien-3-yl), triazolyl, and triazinyl.

The term “heterocycloalkane,” or “heterocycloalkyl,” or “heterocycloalkylene,” as used herein, means monocyclic or bridged three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S and zero double bonds. The monocyclic and bridged heterocycloalkane are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the rings. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be quaternized. Representative examples of heterocycloalkane groups include, but are not limited to, morpholinyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, dioxolanyl, tetrahydrofuranyl,

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thiomorpholinyl, 1,4-dioxanyl, tetrahydrothienyl, tetrahydrothiopyranyl, oxetanyl, piperazinyl, imidazolidinyl, azetidine, azepanyl, aziridinyl, diazepanyl, dithiolanyl, dithianyl, isoxazolidinyl, isothiazolidinyl, oxadiazolidinyl, oxazolidinyl, pyrazolidinyl, tetrahydrothienyl, thiadiazolidinyl, thiazolidinyl, thiomorpholinyl, trithianyl, and trithianyl.

The term “heterocycloalkene,” or “heterocycloalkenyl,” or “heterocycloalkenylene,” as used herein, means monocyclic or bridged three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S and one or more double bonds. The monocyclic and bridged heterocycloalkene are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the rings. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be oxidized and the nitrogen atoms may optionally be quarternized. Representative examples of heterocycloalkene groups include, but are not limited to, 1,4,5,6-tetrahydropyridazinyl, 1,2,3,6-tetrahydropyridinyl, dihydropyranyl, imidazolyl, isothiazolyl, oxadiazolyl, isoxazolyl, oxazolyl, pyranyl, pyrazolyl, pyrrolinyl, thiadiazolyl, thiazolyl, and thiopyranyl.

The term “phenyl,” as used herein, means a monovalent radical formed by removal of a hydrogen atom from benzene.

The term “phenylene,” as used herein, means a divalent radical formed by removal of a hydrogen atom from phenyl.

The term “spiroalkyl,” as used herein, means alkylene, both ends of which are attached to the same carbon atom and is exemplified by C<sub>2</sub>-spiroalkyl, C<sub>3</sub>-spiroalkyl, C<sub>4</sub>-spiroalkyl, C<sub>5</sub>-spiroalkyl, C<sub>6</sub>-spiroalkyl, C<sub>7</sub>-spiroalkyl, C<sub>8</sub>-spiroalkyl, C<sub>9</sub>-spiroalkyl and the like.

The term “spiroheteroalkyl,” as used herein, means spiroalkyl having one or two CH<sub>2</sub> moieties replaced with independently selected O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties unreplaced or replaced with N.

The term “spiroheteroalkenyl,” as used herein, means spiroalkenyl having one or two CH<sub>2</sub> moieties replaced with independently selected O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties unreplaced or replaced with N and also means spiroalkenyl having one or two CH<sub>2</sub> moieties unreplaced or replaced with independently selected O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties replaced with N.

The term “C<sub>2</sub>-C<sub>5</sub>-spiroalkyl,” as used herein, means C<sub>2</sub>-spiroalkyl, C<sub>3</sub>-spiroalkyl, C<sub>4</sub>-spiroalkyl, and C<sub>5</sub>-spiroalkyl.

The term “C<sub>2</sub>-spiroalkyl,” as used herein, means eth-1,2-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term “C<sub>3</sub>-spiroalkyl,” as used herein, means prop-1,3-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term “C<sub>4</sub>-spiroalkyl,” as used herein, means but-1,4-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term “C<sub>5</sub>-spiroalkyl,” as used herein, means pent-1,5-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term “C<sub>6</sub>-spiroalkyl,” as used herein, means hex-1,6-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term “NH protecting group,” as used herein, means trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzylloxycarbonyl, para-nitrobenzylcarbonyl, ortho-bromobenzylloxycarbonyl, chloroacetyl, dichloroacetyl, trichloroacetyl,

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trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amylloxycarbonyl, tert-butoxycarbonyl, para-methoxybenzylloxycarbonyl, 3,4-dimethoxybenzylloxycarbonyl, 4-(phenylazo)benzylloxycarbonyl, 2-furfuryloxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxy-carbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantylloxycarbonyl, 8-quinolyloxycarbonyl, benzyl, diphenylmethyl, triphenylmethyl, 2-nitrophenylthio, methanesulfonyl, para-toluenesulfonyl, N,N-dimethylaminomethylene, benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthyl-methylene, 3-hydroxy-4-pyridylmethylene, cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxocyclohexylidene, diphenylphosphoryl, dibenzylphosphoryl, 5-methyl-2-oxo-2H-1,3-dioxol-4-yl-methyl, trimethylsilyl, triethylsilyl, and triphenylsilyl.

The term “C(O)OH protecting group,” as used herein, means methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, tert-butyl, phenyl, naphthyl, benzyl, diphenylmethyl, triphenylmethyl, para-nitrobenzyl, para-methoxybenzyl, bis(para-methoxyphenyl)methyl, acetyl-methyl, benzoylmethyl, para-nitrobenzoylmethyl, para-bromobenzoylmethyl, para-methanesulfonylbzoylmethyl, 2-tetrahydropyranyl 2-tetrahydrofuranlyl, 2,2,2-trichloro-ethyl, 2-(trimethylsilyl)ethyl, acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, phthalimidomethyl, succinimidomethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, methylthiomethyl, 2-methylthioethyl, phenylthiomethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyl-dimethylsilyl, tert-butyl-diphenylsilyl, diphenylmethylsilyl, and tert-butyl-methoxyphenylsilyl.

The term “OH or SH protecting group,” as used herein, means benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantylloxycarbonyl, vinylloxycarbonyl, allyloxycarbonyl, S-benzylthiocarbonyl, 4-ethoxy-1-naphthylloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl, methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl (phenylmethyl), para-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyl-dimethylsilyl, tert-butyl-diphenylsilyl, diphenylmethylsilyl, and tert-butylmethoxyphenylsilyl.

Compounds

Geometric isomers may exist in the present compounds. Compounds of this invention may contain carbon-carbon double bonds or carbon-nitrogen double bonds in the E or Z configuration, wherein the term “E” represents higher order substituents on opposite sides of the carbon-carbon or car-



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bon-nitrogen double bond and the term “Z” represents higher order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond as determined by the Cahn-Ingold-Prelog Priority Rules. The compounds of this invention may also exist as a mixture of “E” and “Z” isomers. Substituents around a cycloalkyl or heterocycloalkyl are designated as being of cis or trans configuration. Furthermore, the invention contemplates the various isomers and mixtures thereof resulting from the disposal of substituents around an adamantane ring system. Two substituents around a single ring within an adamantane ring system are designated as being of Z or E relative configuration. For examples, see C. D. Jones, M. Kaselj, R. N. Salvatore, W. J. le Noble *J. Org. Chem.* 1998, 63, 2758-2760.

Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms “R” and “S” are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

#### Isotope Enriched or Labeled Compounds

Compounds of the invention can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ ,  $^{36}\text{Cl}$ , and  $^{125}\text{I}$ . Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

In another embodiment, the isotope-labeled compounds contain deuterium ( $^2\text{H}$ ), tritium ( $^3\text{H}$ ) or  $^{14}\text{C}$  isotopes. Isotope-labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotope-labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples disclosed herein and Schemes by substituting a readily available isotope-labeled reagent for a non-labeled reagent. In some instances, compounds may be treated with isotope-labeled reagents to exchange a normal atom with its isotope, for example, hydrogen for deuterium can be exchanged by the action of a deuterio acid such as  $\text{D}_2\text{SO}_4/\text{D}_2\text{O}$ . In addition to the above, relevant procedures and intermediates are disclosed, for instance, in Lizondo, J et al., *Drugs Fut.* 21(11), 1116 (1996); Brickner, S J et al., *J Med Chem.* 39(3), 673 (1996); Mallesham, B et al., *Org Lett.* 5(7), 963 (2003); PCT publications WO1997010223, WO2005099353, WO1995007271, WO2006008754; U.S. Pat. Nos. 7,538,189; 7,534,814; 7,531,685; 7,528,131; 7,521,421; 7,514,068; 7,511,013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; and 20090082471, the methods are hereby incorporated by reference.

The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of Bcl-2 inhibitors in binding assays. Isotope containing compounds

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have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the nonisotope-labeled parent compound (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., *Advances in Drug Research* Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al., *J. Labelled Comp. Radiopharmaceut.*, 36(10):927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999)).

In addition, non-radio active isotope containing drugs, such as deuterated drugs called “heavy drugs,” can be used for the treatment of diseases and conditions related to Bcl-2 activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %. Replacement of up to about 15% of normal atom with a heavy isotope has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, *Ann. N.Y. Acad. Sci.* 1960 84: 770; Thomson J F, *Ann. New York Acad. Sci.* 1960 84: 736; Czajka D M et al., *Am. J. Physiol.* 1961 201: 357). Acute replacement of as high as 15%-23% in human fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in “Dosimetry & Treatment Planning for Neutron Capture Therapy”, Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp. 125-134; *Diabetes Metab.* 23: 251 (1997)).

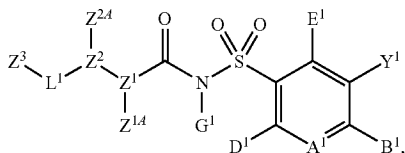
Stable isotope labeling of a drug can alter its physicochemical properties such as pKa and lipid solubility. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. Accordingly, the incorporation of an isotope at a site of metabolism or enzymatic transformation will slow said reactions potentially altering the pharmacokinetic profile or efficacy relative to the non-isotopic compound.

Suitable groups for  $\text{A}^1$ ,  $\text{B}^1$ ,  $\text{D}^1$ ,  $\text{E}^1$ ,  $\text{G}^1$ ,  $\text{Y}^1$ ,  $\text{L}^1$ ,  $\text{Z}^{1A}$ ,  $\text{Z}^{2A}$ ,  $\text{Z}^1$ ,  $\text{Z}^2$ , and  $\text{Z}^3$  in compounds of Formula (I) are independently selected. The described embodiments of the present invention may be combined. Such combination is contemplated and within the scope of the present invention. For example, it is contemplated that embodiments for any of  $\text{A}^1$ ,  $\text{B}^1$ ,  $\text{D}^1$ ,  $\text{E}^1$ ,  $\text{G}^1$ ,  $\text{Y}^1$ ,  $\text{L}^1$ ,  $\text{Z}^{1A}$ ,  $\text{Z}^{2A}$ ,  $\text{Z}^1$ ,  $\text{Z}^2$ , and  $\text{Z}^3$  can be combined with embodiments defined for any other of  $\text{A}^1$ ,  $\text{B}^1$ ,  $\text{D}^1$ ,  $\text{E}^1$ ,  $\text{G}^1$ ,  $\text{Y}^1$ ,  $\text{L}^1$ ,  $\text{Z}^{1A}$ ,  $\text{Z}^{2A}$ ,  $\text{Z}^1$ ,  $\text{Z}^2$ , and  $\text{Z}^3$ .

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (I)

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wherein

A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOH, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

B<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOH, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

D<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOH, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

E<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOH, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, C(O)OH, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, C(O)R<sup>17</sup>, C(O)OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, NH<sub>2</sub>, NHR<sup>17</sup>, N(R<sup>17</sup>)<sub>2</sub>, NHC(O)R<sup>17</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>17</sup>, C(O)N(R<sup>17</sup>)<sub>2</sub>, NHS(O)R<sup>17</sup> or NHSO<sub>2</sub>R<sup>17</sup>; or

E<sup>1</sup> and Y<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

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(I) A<sup>2</sup>, B<sup>1</sup>, and D<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOH, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOH, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

A<sup>2</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOH, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

A<sup>2</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

B<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOH, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

G<sup>1</sup> is H, or C(O)OR;

R is alkyl;

R<sup>1</sup> is R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup>;

R<sup>1,4</sup> is cycloalkyl, cycloalkenyl or cycloalkynyl;

R<sup>2</sup> is phenyl, which is unfused or fused with R<sup>2,4</sup>; R<sup>2,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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R<sup>3</sup> is heteroaryl, which is unfused or fused with R<sup>3A</sup>; R<sup>3A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>4A</sup>; R<sup>4A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>5</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>6</sup>, NC(R<sup>6A</sup>)(R<sup>6B</sup>), R<sup>7</sup>, OR<sup>7</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, C(O)R<sup>7</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>7</sup>, C(O)N(R<sup>7</sup>)<sub>2</sub>, NHC(O)R<sup>7</sup>, NR<sup>7</sup>C(O)R<sup>7</sup>, NHSO<sub>2</sub>R<sup>7</sup>, NHC(O)OR<sup>7</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>7</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>7</sup>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NHR<sup>7</sup>, OH, (O), C(O)OH, N<sub>3</sub>, CN, NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>6</sup> is C<sub>2</sub>-C<sub>5</sub>-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N<sub>3</sub>, CN, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, NH<sub>2</sub>, NH(CH<sub>3</sub>) or N(CH<sub>3</sub>)<sub>2</sub>;

R<sup>6A</sup> and R<sup>6B</sup> are independently selected alkyl or, together with the N to which they are attached, R<sup>6C</sup>;

R<sup>6C</sup> is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH<sub>2</sub> moiety unreplaced or replaced with O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup>;

R<sup>8</sup> is phenyl, which is unfused or fused with R<sup>8A</sup>; R<sup>8A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>9</sup> is heteroaryl, which is unfused or fused with R<sup>9A</sup>; R<sup>9A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>10A</sup>; R<sup>10A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>11</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup>, SR<sup>12</sup>, SS(O)R<sup>12</sup>, SO<sub>2</sub>R<sup>12</sup>, C(O)R<sup>12</sup>, CO(O)R<sup>12</sup>, OC(O)R<sup>12</sup>, OC(O)OR<sup>12</sup>, NH<sub>2</sub>, NHR<sup>12</sup>, N(R<sup>12</sup>)<sub>2</sub>, NHC(O)R<sup>12</sup>, NR<sup>12</sup>C(O)R<sup>12</sup>, NHS(O)<sub>2</sub>R<sup>12</sup>, NR<sup>12</sup>S(O)<sub>2</sub>R<sup>12</sup>, NHC(O)OR<sup>12</sup>, NR<sup>12</sup>C(O)OR<sup>12</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>12</sup>, NHC(O)N(R<sup>12</sup>)<sub>2</sub>, NR<sup>12</sup>C(O)NHR<sup>12</sup>, NR<sup>12</sup>C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>12</sup>, C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>12</sup>, C(O)NHSO<sub>2</sub>R<sup>12</sup>, C(O)NR<sup>12</sup>SO<sub>2</sub>R<sup>12</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>12</sup>, SO<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>12</sup>, C(N)N(R<sup>12</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>12</sup> is R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> or R<sup>16</sup>;

R<sup>13</sup> is phenyl, which is unfused or fused with R<sup>13A</sup>; R<sup>13A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>14</sup> is heteroaryl, which is unfused or fused with R<sup>14A</sup>; R<sup>14A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>15</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R<sup>15A</sup>; R<sup>15A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>16</sup> is alkyl, alkenyl or alkynyl;

R<sup>17</sup> is R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> or R<sup>21</sup>;

R<sup>18</sup> is phenyl, which is unfused or fused with R<sup>18A</sup>; R<sup>18A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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R<sup>19</sup> is heteroaryl, which is unfused or fused with R<sup>19A</sup>; R<sup>19A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>20</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R<sup>20A</sup>; R<sup>20A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>21</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, OR<sup>22</sup>, SR<sup>22</sup>, S(O)R<sup>22</sup>, SO<sub>2</sub>R<sup>22</sup>, C(O)R<sup>22</sup>, CO(O)R<sup>22</sup>, OC(O)R<sup>22</sup>, OC(O)OR<sup>22</sup>, NH<sub>2</sub>, NHR<sup>22</sup>, N(R<sup>22</sup>)<sub>2</sub>, NHC(O)R<sup>22</sup>, NR<sup>22</sup>C(O)R<sup>22</sup>, NHS(O)<sub>2</sub>R<sup>22</sup>, NR<sup>22</sup>S(O)<sub>2</sub>R<sup>22</sup>, NHC(O)OR<sup>22</sup>, NR<sup>22</sup>C(O)OR<sup>22</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>22</sup>, NHC(O)N(R<sup>22</sup>)<sub>2</sub>, NR<sup>22</sup>C(O)NHR<sup>22</sup>, NR<sup>22</sup>C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>22</sup>, C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>22</sup>, C(O)NHSO<sub>2</sub>R<sup>22</sup>, C(O)NR<sup>22</sup>SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>22</sup>, SO<sub>2</sub>N(R<sup>22</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>22</sup>, C(N)N(R<sup>22</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>23</sup>, R<sup>24</sup> or R<sup>25</sup>;

R<sup>23</sup> is phenyl, which is unfused or fused with R<sup>23A</sup>; R<sup>23A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>24</sup> is heteroarene, which is unfused or fused with R<sup>24A</sup>; R<sup>24A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>25</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>25A</sup>; R<sup>25A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z<sup>1</sup> is R<sup>26</sup> or R<sup>27</sup>;

Z<sup>2</sup> is R<sup>28</sup>, R<sup>29</sup> or R<sup>30</sup>;

Z<sup>1A</sup> and Z<sup>2A</sup> are both absent or are taken together to form CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub> or Z<sup>12A</sup>;

Z<sup>12A</sup> is C<sub>2</sub>-C<sub>6</sub>-alkylene alkylene having one or two CH<sub>2</sub> moieties replaced by NH, N(CH<sub>3</sub>), S, S(O) or SO<sub>2</sub>;

L<sup>1</sup> is a R<sup>37</sup>, OR<sup>37</sup>, SR<sup>37</sup>, S(O)R<sup>37</sup>, SO<sub>2</sub>R<sup>37</sup>, C(O)R<sup>37</sup>, CO(O)R<sup>37</sup>, OC(O)R<sup>37</sup>, OC(O)OR<sup>37</sup>, NHR<sup>37</sup>, C(O)NH, C(O)NR<sup>37</sup>, C(O)NHOR<sup>37</sup>, C(O)NHSO<sub>2</sub>R<sup>37</sup>, SO<sub>2</sub>NH, SO<sub>2</sub>NHR<sup>37</sup>, C(N)NH, C(N)NHR<sup>37</sup>;

R<sup>26</sup> is phenylene, which is unfused or fused with R<sup>26A</sup>; R<sup>26A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>27</sup> is heteroarylene, which is unfused or fused with R<sup>27A</sup>; R<sup>27A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>28</sup> is phenylene, which is unfused or fused with R<sup>28A</sup>; R<sup>28A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>29</sup> is heteroarylene, which is unfused or fused with R<sup>29A</sup>; R<sup>29A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>30</sup> is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R<sup>30A</sup>; R<sup>30A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>37</sup> is a bond or R<sup>37A</sup>;

R<sup>37A</sup> is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R<sup>37B</sup>, OR<sup>37B</sup>, SR<sup>37B</sup>, S(O)R<sup>37B</sup>, SO<sub>2</sub>R<sup>37B</sup>, C(O)R<sup>37B</sup>, CO(O)R<sup>37B</sup>, OC(O)R<sup>37B</sup>, OC(O)OR<sup>37B</sup>, NH<sub>2</sub>, NHR<sup>37B</sup>, N(R<sup>37B</sup>)<sub>2</sub>, NHC(O)R<sup>37B</sup>, NR<sup>37B</sup>C(O)R<sup>37B</sup>, NHS(O)<sub>2</sub>R<sup>37B</sup>, NR<sup>37B</sup>S(O)<sub>2</sub>R<sup>37B</sup>, NHC(O)OR<sup>37B</sup>, NR<sup>37B</sup>C(O)OR<sup>37B</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>37B</sup>, NHC(O)N(R<sup>37B</sup>)<sub>2</sub>, NR<sup>37B</sup>C(O)NHR<sup>37B</sup>, NR<sup>37B</sup>C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>37B</sup>, C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>37B</sup>, C(O)



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NHSO<sub>2</sub>R<sup>37B</sup>, C(O)NR<sup>37B</sup>SO<sub>2</sub>R<sup>37B</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>37B</sup>, SO<sub>2</sub>N(R<sup>37B</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>37B</sup>, C(N)N(R<sup>37B</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br and I substituents; R<sup>37B</sup> is alkyl, alkenyl, alkynyl, or R<sup>37C</sup>;

R<sup>37C</sup> is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

Z<sup>3</sup> is R<sup>38</sup>, R<sup>39</sup> or R<sup>40</sup>;

R<sup>38</sup> is phenyl, which is unfused or fused with R<sup>38A</sup>; R<sup>38A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>39</sup> is heteroaryl, which is unfused or fused with R<sup>39A</sup>; R<sup>39A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>40</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>40A</sup>; R<sup>40A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R<sup>26</sup> and R<sup>27</sup> are substituted (i.e., if Z<sup>1A</sup> and Z<sup>2A</sup> are absent) or further substituted (i.e., if Z<sup>1A</sup> and Z<sup>2A</sup> are present) with R<sup>41</sup>, OR<sup>41</sup>, SR<sup>41</sup>, S(O)R<sup>41</sup>, SO<sub>2</sub>R<sup>41</sup>, C(O)R<sup>41</sup>, CO(O)R<sup>41</sup>, OC(O)R<sup>41</sup>, OC(O)OR<sup>41</sup>, NHR<sup>41</sup>, N(R<sup>41</sup>)<sub>2</sub>, NHC(O)R<sup>41</sup>, NR<sup>41</sup>C(O)R<sup>41</sup>, NHS(O)<sub>2</sub>R<sup>41</sup>, NR<sup>41</sup>S(O)<sub>2</sub>R<sup>41</sup>, NHC(O)OR<sup>41</sup>, NR<sup>41</sup>C(O)OR<sup>41</sup>, NHC(O)NHR<sup>41</sup>, NHC(O)N(R<sup>41</sup>)<sub>2</sub>, NR<sup>41</sup>C(O)NHR<sup>41</sup>, NR<sup>41</sup>C(O)N(R<sup>41</sup>)<sub>2</sub>, C(O)NHR<sup>41</sup>, C(O)N(R<sup>41</sup>)<sub>2</sub>, C(O)NHOR<sup>41</sup>, C(O)NHSO<sub>2</sub>R<sup>41</sup>, C(O)NR<sup>41</sup>SO<sub>2</sub>R<sup>41</sup>, SO<sub>2</sub>NHR<sup>41</sup>, SO<sub>2</sub>N(R<sup>41</sup>)<sub>2</sub>, C(N)NHR<sup>41</sup>, or C(N)N(R<sup>41</sup>)<sub>2</sub>;

R<sup>41</sup> is heteroaryl, which is fused with R<sup>43A</sup>; R<sup>43A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused or fused with benzene, heteroarene or R<sup>43B</sup>; R<sup>43B</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by E<sup>1</sup> and Y<sup>1</sup> together, Y<sup>1</sup> and B<sup>1</sup> together, A<sup>2</sup> and B<sup>1</sup> together, A<sup>2</sup> and D<sup>1</sup> together, R<sup>1A</sup>, R<sup>2</sup>, R<sup>2A</sup>, R<sup>3</sup>, R<sup>3A</sup>, R<sup>4</sup>, R<sup>4A</sup>, R<sup>6</sup>, R<sup>6C</sup>, R<sup>8</sup>, R<sup>8A</sup>, R<sup>9</sup>, R<sup>9A</sup>, R<sup>10</sup>, R<sup>10A</sup>, R<sup>13</sup>, R<sup>13A</sup>, R<sup>14</sup>, R<sup>14A</sup>, R<sup>15</sup>, R<sup>15A</sup>, R<sup>18</sup>, R<sup>18A</sup>, R<sup>19</sup>, R<sup>19A</sup>, R<sup>20</sup>, R<sup>20A</sup>, R<sup>23</sup>, R<sup>23A</sup>, R<sup>24</sup>, R<sup>24A</sup>, R<sup>25</sup>, R<sup>25A</sup>, R<sup>26</sup>, R<sup>26A</sup>, R<sup>27</sup>, R<sup>27A</sup>, R<sup>28</sup>, R<sup>28A</sup>, R<sup>29</sup>, R<sup>29A</sup>, R<sup>30</sup>, R<sup>30A</sup>, R<sup>37B</sup>, R<sup>38</sup>, R<sup>38A</sup>, R<sup>39</sup>, R<sup>39A</sup>, R<sup>40</sup>, and R<sup>40A</sup> are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SR<sup>57</sup>, S(O)R<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, OC(O)R<sup>57</sup>, OC(O)OR<sup>57</sup>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NR<sup>57</sup>C(O)R<sup>57</sup>, NHS(O)<sub>2</sub>R<sup>57</sup>, NR<sup>57</sup>S(O)<sub>2</sub>R<sup>57</sup>, NHC(O)OR<sup>57</sup>, NR<sup>57</sup>C(O)OR<sup>57</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>57</sup>, NHC(O)N(R<sup>57</sup>)<sub>2</sub>, NR<sup>57</sup>C(O)NHR<sup>57</sup>, NR<sup>57</sup>C(O)N(R<sup>57</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>57</sup>, C(O)NHSO<sub>2</sub>R<sup>57</sup>, C(O)NR<sup>57</sup>SO<sub>2</sub>R<sup>57</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>57</sup>, SO<sub>2</sub>N(R<sup>57</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>57</sup>, C(N)N(R<sup>57</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;

R<sup>57</sup> is R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup> or R<sup>61</sup>;

R<sup>58</sup> is phenyl, which is unfused or fused with R<sup>58A</sup>; R<sup>58A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>59</sup> is heteroaryl, which is unfused or fused with R<sup>59A</sup>; R<sup>59A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>60</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>60A</sup>; R<sup>60A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>61</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently

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selected R<sup>62</sup>, OR<sup>62</sup>, SR<sup>62</sup>, S(O)R<sup>62</sup>, SO<sub>2</sub>R<sup>62</sup>, C(O)R<sup>62</sup>, CO(O)R<sup>62</sup>, OC(O)R<sup>62</sup>, OC(O)OR<sup>62</sup>, NH<sub>2</sub>, NHR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, NHC(O)R<sup>62</sup>, NR<sup>62</sup>C(O)R<sup>62</sup>, NHS(O)<sub>2</sub>R<sup>62</sup>, NR<sup>62</sup>S(O)<sub>2</sub>R<sup>62</sup>, NHC(O)OR<sup>62</sup>, NR<sup>62</sup>C(O)OR<sup>62</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>62</sup>, NHC(O)N(R<sup>62</sup>)<sub>2</sub>, NR<sup>62</sup>C(O)NHR<sup>62</sup>, NR<sup>62</sup>C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>62</sup>, C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>62</sup>, C(O)NHSO<sub>2</sub>R<sup>62</sup>, C(O)NR<sup>62</sup>SO<sub>2</sub>R<sup>62</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>62</sup>, SO<sub>2</sub>N(R<sup>62</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>62</sup>, C(N)N(R<sup>62</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>62</sup> is R<sup>63</sup>, R<sup>64</sup>, R<sup>65</sup> or R<sup>66</sup>;

R<sup>63</sup> is phenyl, which is unfused or fused with R<sup>63A</sup>; R<sup>63A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>64</sup> is heteroaryl, which is unfused or fused with R<sup>64A</sup>; R<sup>64A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>65</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with R<sup>65A</sup>; R<sup>65A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>66</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>67</sup>, OR<sup>67</sup>, SR<sup>67</sup>, S(O)R<sup>67</sup>, SO<sub>2</sub>R<sup>67</sup>, C(O)R<sup>67</sup>, CO(O)R<sup>67</sup>, OC(O)R<sup>67</sup>, OC(O)OR<sup>67</sup>, NH<sub>2</sub>, NHR<sup>67</sup>, N(R<sup>67</sup>)<sub>2</sub>, NHC(O)R<sup>67</sup>, NR<sup>67</sup>C(O)R<sup>67</sup>, NHS(O)<sub>2</sub>R<sup>67</sup>, NR<sup>67</sup>S(O)<sub>2</sub>R<sup>67</sup>, NHC(O)OR<sup>67</sup>, NR<sup>67</sup>C(O)OR<sup>67</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>67</sup>, NHC(O)N(R<sup>67</sup>)<sub>2</sub>, NR<sup>67</sup>C(O)NHR<sup>67</sup>, NR<sup>67</sup>C(O)N(R<sup>67</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>67</sup>, C(O)N(R<sup>67</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>67</sup>, C(O)NHSO<sub>2</sub>R<sup>67</sup>, C(O)NR<sup>67</sup>SO<sub>2</sub>R<sup>67</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>67</sup>, SO<sub>2</sub>N(R<sup>67</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>67</sup>, C(N)N(R<sup>67</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I substituents;

R<sup>67</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup>, R<sup>63</sup>, R<sup>64</sup>, R<sup>65</sup>, and R<sup>67</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, OR<sup>68</sup>, SR<sup>68</sup>, S(O)R<sup>68</sup>, SO<sub>2</sub>R<sup>68</sup>, C(O)R<sup>68</sup>, CO(O)R<sup>68</sup>, OC(O)R<sup>68</sup>, OC(O)OR<sup>68</sup>, NH<sub>2</sub>, NHR<sup>68</sup>, N(R<sup>68</sup>)<sub>2</sub>, NHC(O)R<sup>68</sup>, NR<sup>68</sup>C(O)R<sup>68</sup>, NHS(O)<sub>2</sub>R<sup>68</sup>, NR<sup>68</sup>S(O)<sub>2</sub>R<sup>68</sup>, NHC(O)OR<sup>68</sup>, NR<sup>68</sup>C(O)OR<sup>68</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>68</sup>, NHC(O)N(R<sup>68</sup>)<sub>2</sub>, NR<sup>68</sup>C(O)NHR<sup>68</sup>, NR<sup>68</sup>C(O)N(R<sup>68</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>68</sup>, C(O)N(R<sup>68</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>68</sup>, C(O)NHSO<sub>2</sub>R<sup>68</sup>, C(O)NR<sup>68</sup>SO<sub>2</sub>R<sup>68</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>68</sup>, SO<sub>2</sub>N(R<sup>68</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>68</sup>, C(N)N(R<sup>68</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>68</sup> is R<sup>69</sup>, R<sup>70</sup>, R<sup>71</sup> or R<sup>72</sup>;

R<sup>69</sup> is phenyl, which is unfused or fused with R<sup>69A</sup>; R<sup>69A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>70</sup> is heteroaryl, which is unfused or fused with R<sup>70A</sup>; R<sup>70A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>71</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>71A</sup>; R<sup>71A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>72</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>73</sup>, OR<sup>73</sup>, SR<sup>73</sup>, S(O)R<sup>73</sup>, SO<sub>2</sub>R<sup>73</sup>, C(O)R<sup>73</sup>, CO(O)R<sup>73</sup>, OC(O)R<sup>73</sup>, OC(O)OR<sup>73</sup>, NH<sub>2</sub>, NHR<sup>73</sup>, N(R<sup>73</sup>)<sub>2</sub>, NHC(O)R<sup>73</sup>, NR<sup>73</sup>C(O)R<sup>73</sup>, NI(SO)<sub>2</sub>R<sup>73</sup>, NR<sup>73</sup>S(O)<sub>2</sub>R<sup>73</sup>,

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NHC(O)OR<sup>73</sup>, NR<sup>73</sup>C(O)OR<sup>73</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>73</sup>, NHC(O)N(R<sup>73</sup>)<sub>2</sub>, NR<sup>73</sup>C(O)NHR<sup>73</sup>, NR<sup>73</sup>C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>73</sup>, C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>73</sup>, C(O)NHSO<sub>2</sub>R<sup>73</sup>, C(O)NR<sup>73</sup>SO<sub>2</sub>R<sup>73</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>73</sup>, SO<sub>2</sub>N(R<sup>73</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>73</sup>, C(N)N(R<sup>73</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>73</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R<sup>69</sup>, R<sup>70</sup>, and R<sup>71</sup> are unsubstituted or substituted with one or two or three or four of independently selected NH<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I.

Another embodiment of this invention pertains to compounds of Formula (I), wherein

A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

B<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

D<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

E<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

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SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, C(O)OH, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, C(O)R<sup>17</sup>, C(O)OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, NH<sub>2</sub>, NHR<sup>17</sup>, N(R<sup>17</sup>)<sub>2</sub>, NHC(O)R<sup>17</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>17</sup>, C(O)N(R<sup>17</sup>)<sub>2</sub>, NHS(O)R<sup>17</sup> or NHSO<sub>2</sub>R<sup>17</sup>; or

E<sup>1</sup> and Y<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, B<sup>1</sup>, and D<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

A<sup>2</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

A<sup>2</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

B<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

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NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

G<sup>1</sup> is H, or C(O)OR;

R is alkyl;

R<sup>1</sup> is R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup>;

R<sup>1,4</sup> is cycloalkyl, cycloalkenyl or cycloalkynyl;

R<sup>2</sup> is phenyl, which is unfused or fused with R<sup>2,4</sup>; R<sup>2,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>3</sup> is heteroaryl, which is unfused or fused with R<sup>3,4</sup>; R<sup>3,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>4,4</sup>; R<sup>4,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>5</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>6</sup>, NC(R<sup>6A</sup>)(R<sup>6B</sup>), R<sup>7</sup>, OR<sup>7</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, C(O)R<sup>7</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>7</sup>, C(O)N(R<sup>7</sup>)<sub>2</sub>, NHC(O)R<sup>7</sup>, NR<sup>7</sup>C(O)R<sup>7</sup>, NHSO<sub>2</sub>R<sup>7</sup>, NHC(O)OR<sup>7</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>7</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>7</sup>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NHR<sup>7</sup>, OH, (O), C(O)OH, N<sub>3</sub>, CN, NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>6</sup> is C<sub>2</sub>-C<sub>5</sub>-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N<sub>3</sub>, CN, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, NH<sub>2</sub>, NH(CH<sub>3</sub>) or N(CH<sub>3</sub>)<sub>2</sub>;

R<sup>6A</sup> and R<sup>6B</sup> are independently selected alkyl or, together with the N to which they are attached, R<sup>6C</sup>;

R<sup>6C</sup> is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH<sub>2</sub> moiety unreplaced or replaced with O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup>;

R<sup>8</sup> is phenyl, which is unfused or fused with R<sup>8,4</sup>; R<sup>8,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>9</sup> is heteroaryl, which is unfused or fused with R<sup>9,4</sup>; R<sup>9,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>10,4</sup>; R<sup>10,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>11</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup>, SR<sup>12</sup>, S(O)R<sup>12</sup>, SO<sub>2</sub>R<sup>12</sup>, C(O)R<sup>12</sup>, CO(O)R<sup>12</sup>, OC(O)R<sup>12</sup>, OC(O)OR<sup>12</sup>, NH<sub>2</sub>, NHR<sup>12</sup>, N(R<sup>12</sup>)<sub>2</sub>, NHC(O)R<sup>12</sup>, NR<sup>12</sup>C(O)R<sup>12</sup>, NHS(O)<sub>2</sub>R<sup>12</sup>, NR<sup>12</sup>S(O)<sub>2</sub>R<sup>12</sup>, NHC(O)OR<sup>12</sup>, NR<sup>12</sup>C(O)OR<sup>12</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>12</sup>, NHC(O)N(R<sup>12</sup>)<sub>2</sub>, NR<sup>12</sup>C(O)NHR<sup>12</sup>, NR<sup>12</sup>C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>12</sup>, C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>12</sup>, C(O)NHSO<sub>2</sub>R<sup>12</sup>, C(O)NR<sup>12</sup>SO<sub>2</sub>R<sup>12</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>12</sup>, SO<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>12</sup>, C(N)N(R<sup>12</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>12</sup> is R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> or R<sup>16</sup>;

R<sup>13</sup> is phenyl, which is unfused or fused with R<sup>13,4</sup>; R<sup>13,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>14</sup> is heteroaryl, which is unfused or fused with R<sup>14,4</sup>; R<sup>14,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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R<sup>15</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R<sup>15,4</sup>; R<sup>15,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>16</sup> is alkyl, alkenyl or alkynyl;

R<sup>17</sup> is R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> or R<sup>21</sup>;

R<sup>18</sup> is phenyl, which is unfused or fused with R<sup>18,4</sup>; R<sup>18,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>19</sup> is heteroaryl, which is unfused or fused with R<sup>19,4</sup>; R<sup>19,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>20</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R<sup>20,4</sup>; R<sup>20,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>21</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, OR<sup>22</sup>, SR<sup>22</sup>, S(O)R<sup>22</sup>, SO<sub>2</sub>R<sup>22</sup>, C(O)R<sup>22</sup>, CO(O)R<sup>22</sup>, OC(O)R<sup>22</sup>, OC(O)OR<sup>22</sup>, NH<sub>2</sub>, NHR<sup>22</sup>, N(R<sup>22</sup>)<sub>2</sub>, NHC(O)R<sup>22</sup>, NR<sup>22</sup>C(O)R<sup>22</sup>, NHS(O)<sub>2</sub>R<sup>22</sup>, NR<sup>22</sup>S(O)<sub>2</sub>R<sup>22</sup>, NHC(O)OR<sup>22</sup>, NR<sup>22</sup>C(O)OR<sup>22</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>22</sup>, NHC(O)N(R<sup>22</sup>)<sub>2</sub>, NR<sup>22</sup>C(O)NHR<sup>22</sup>, NR<sup>22</sup>C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>22</sup>, C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>22</sup>, C(O)NHSO<sub>2</sub>R<sup>22</sup>, C(O)NR<sup>22</sup>SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>22</sup>, SO<sub>2</sub>N(R<sup>22</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>22</sup>, C(N)N(R<sup>22</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>23</sup>, R<sup>24</sup> or R<sup>25</sup>;

R<sup>23</sup> is phenyl, which is unfused or fused with R<sup>23,4</sup>; R<sup>23,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>24</sup> is heteroarene, which is unfused or fused with R<sup>24,4</sup>; R<sup>24,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>25</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>25,4</sup>; R<sup>25,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z<sup>1</sup> is R<sup>26</sup> or R<sup>27</sup>;

Z<sup>2</sup> is R<sup>28</sup>, R<sup>29</sup> or R<sup>30</sup>;

Z<sup>1,4</sup> and Z<sup>2,4</sup> are both absent or are taken together to form CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub> or Z<sup>12,4</sup>;

Z<sup>12,4</sup> is C<sub>2</sub>-C<sub>6</sub>-alkylene having one or two CH<sub>2</sub> moieties replaced by NH, N(CH<sub>3</sub>), S, S(O) or SO<sub>2</sub>;

L<sup>1</sup> is a R<sup>37</sup>, OR<sup>37</sup>, SR<sup>37</sup>, S(O)R<sup>37</sup>, SO<sub>2</sub>R<sup>37</sup>, C(O)R<sup>37</sup>, CO(O)R<sup>37</sup>, OC(O)R<sup>37</sup>, OC(O)OR<sup>37</sup>, NHR<sup>37</sup>, C(O)NH, C(O)NR<sup>37</sup>, C(O)NHOR<sup>37</sup>, C(O)NHSO<sub>2</sub>R<sup>37</sup>, SO<sub>2</sub>NH, SO<sub>2</sub>NHR<sup>37</sup>, C(N)NH, C(N)NHR<sup>37</sup>;

R<sup>26</sup> is phenylene, which is unfused or fused with R<sup>26,4</sup>; R<sup>26,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>27</sup> is heteroarylene, which is unfused or fused with R<sup>27,4</sup>; R<sup>27,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>28</sup> is phenylene, which is unfused or fused with R<sup>28,4</sup>; R<sup>28,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>29</sup> is heteroarylene, which is unfused or fused with R<sup>29,4</sup>; R<sup>29,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>30</sup> is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R<sup>30,4</sup>; R<sup>30,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;



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$R^{37}$  is a bond or  $R^{37A}$ ;

$R^{37A}$  is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected  $R^{37B}$ ,  $OR^{37B}$ ,  $SR^{37B}$ ,  $S(O)R^{37B}$ ,  $SO_2R^{37B}$ ,  $C(O)R^{37B}$ ,  $CO(O)R^{37B}$ ,  $OC(O)R^{37B}$ ,  $OC(O)OR^{37B}$ ,  $NH_2$ ,  $NHR^{37B}$ ,  $N(R^{37B})_2$ ,  $NHC(O)R^{37B}$ ,  $NR^{37B}C(O)R^{37B}$ ,  $NHS(O)_2R^{37B}$ ,  $NR^{37B}S(O)_2R^{37B}$ ,  $NHC(O)OR^{37B}$ ,  $NR^{37B}C(O)OR^{37B}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{37B}$ ,  $NHC(O)N(R^{37B})_2$ ,  $NR^{37B}C(O)NHR^{37B}$ ,  $NR^{37B}C(O)N(R^{37B})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{37B}$ ,  $C(O)N(R^{37B})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{37B}$ ,  $C(O)NHSO_2R^{37B}$ ,  $C(O)NR^{37B}SO_2R^{37B}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{37B}$ ,  $SO_2N(R^{37B})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{37B}$ ,  $C(N)N(R^{37B})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  and  $I$  substituents;

$R^{37B}$  is alkyl, alkenyl, alkynyl, or  $R^{37C}$ ;

$R^{37C}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

$Z^3$  is  $R^{38}$ ,  $R^{39}$  or  $R^{40}$ ;

$R^{38}$  is phenyl, which is unfused or fused with  $R^{38A}$ ;  $R^{38A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{39}$  is heteroaryl, which is unfused or fused with  $R^{39A}$ ;  $R^{39A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{40}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{40A}$ ;  $R^{40A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by  $R^{26}$  and  $R^{27}$  are substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are absent) or further substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are present) with  $R^{41}$ ,  $OR^{41}$ ,  $SR^{41}$ ,  $S(O)R^{41}$ ,  $SO_2R^{41}$ ,  $C(O)R^{41}$ ,  $CO(O)R^{41}$ ,  $OC(O)R^{41}$ ,  $OC(O)OR^{41}$ ,  $NHR^{41}$ ,  $N(R^{41})_2$ ,  $NHC(O)R^{41}$ ,  $NR^{41}C(O)R^{41}$ ,  $NHS(O)_2R^{41}$ ,  $NR^{41}S(O)_2R^{41}$ ,  $NHC(O)OR^{41}$ ,  $NR^{41}C(O)OR^{41}$ ,  $NHC(O)NHR^{41}$ ,  $NHC(O)N(R^{41})_2$ ,  $NR^{41}C(O)NHR^{41}$ ,  $NR^{41}C(O)N(R^{41})_2$ ,  $C(O)NHR^{41}$ ,  $C(O)N(R^{41})_2$ ,  $C(O)NHOR^{41}$ ,  $C(O)NHSO_2R^{41}$ ,  $C(O)NR^{41}SO_2R^{41}$ ,  $SO_2NHR^{41}$ ,  $SO_2N(R^{41})_2$ ,  $C(N)NHR^{41}$ , or  $C(N)N(R^{41})_2$ ;

$R^{41}$  is heteroaryl, which is fused with  $R^{43A}$ ;  $R^{43A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused;

wherein the cyclic moieties represented by  $E^1$  and  $Y^1$  together,  $Y^1$  and  $B^1$  together,  $A^2$  and  $B^1$  together,  $A^2$  and  $D^1$  together,  $R^{1A}$ ,  $R^2$ ,  $R^{2A}$ ,  $R^3$ ,  $R^{3A}$ ,  $R^4$ ,  $R^{4A}$ ,  $R^6$ ,  $R^{6C}$ ,  $R^8$ ,  $R^{8A}$ ,  $R^9$ ,  $R^{9A}$ ,  $R^{10}$ ,  $R^{10A}$ ,  $R^{13}$ ,  $R^{13A}$ ,  $R^{14}$ ,  $R^{14A}$ ,  $R^{15}$ ,  $R^{15A}$ ,  $R^{18}$ ,  $R^{18A}$ ,  $R^{19}$ ,  $R^{19A}$ ,  $R^{20}$ ,  $R^{20A}$ ,  $R^{23}$ ,  $R^{23A}$ ,  $R^{24}$ ,  $R^{24A}$ ,  $R^{25}$ ,  $R^{25A}$ ,  $R^{26}$ ,  $R^{26A}$ ,  $R^{27}$ ,  $R^{27A}$ ,  $R^{28}$ ,  $R^{28A}$ ,  $R^{29}$ ,  $R^{29A}$ ,  $R^{30}$ ,  $R^{30A}$ ,  $R^{37B}$ ,  $R^{38}$ ,  $R^{38A}$ ,  $R^{39}$ ,  $R^{39A}$ ,  $R^{40}$ , and  $R^{40A}$  are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SR^{57}$ ,  $S(O)R^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $OC(O)R^{57}$ ,  $OC(O)OR^{57}$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NR^{57}C(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $NR^{57}S(O)_2R^{57}$ ,  $NHC(O)OR^{57}$ ,  $NR^{57}C(O)OR^{57}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{57}$ ,  $NHC(O)N(R^{57})_2$ ,  $NR^{57}C(O)NHR^{57}$ ,  $NR^{57}C(O)N(R^{57})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{57}$ ,  $C(O)N(R^{57})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{57}$ ,  $C(O)NHSO_2R^{57}$ ,  $C(O)NR^{57}SO_2R^{57}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{57}$ ,  $SO_2N(R^{57})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{57}$ ,  $C(N)N(R^{57})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$  or  $R^{61}$ ;

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$R^{58}$  is phenyl, which is unfused or fused with  $R^{58A}$ ;  $R^{58A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{59}$  is heteroaryl, which is unfused or fused with  $R^{59A}$ ;  $R^{59A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{60}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{60A}$ ;  $R^{60A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{61}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $SR^{62}$ ,  $S(O)R^{62}$ ,  $SO_2R^{62}$ ,  $C(O)R^{62}$ ,  $CO(O)R^{62}$ ,  $OC(O)R^{62}$ ,  $OC(O)OR^{62}$ ,  $NH_2$ ,  $NHR^{62}$ ,  $N(R^{62})_2$ ,  $NHC(O)R^{62}$ ,  $NR^{62}C(O)R^{62}$ ,  $NHS(O)_2R^{62}$ ,  $NR^{62}S(O)_2R^{62}$ ,  $NHC(O)OR^{62}$ ,  $NR^{62}C(O)OR^{62}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{62}$ ,  $NHC(O)N(R^{62})_2$ ,  $NR^{62}C(O)NHR^{62}$ ,  $NR^{62}C(O)N(R^{62})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{62}$ ,  $C(O)N(R^{62})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{62}$ ,  $C(O)NHSO_2R^{62}$ ,  $C(O)NR^{62}SO_2R^{62}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{62}$ ,  $SO_2N(R^{62})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{62}$ ,  $C(N)N(R^{62})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{62}$  is  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$  or  $R^{66}$ ;

$R^{63}$  is phenyl, which is unfused or fused with  $R^{63A}$ ;  $R^{63A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{64}$  is heteroaryl, which is unfused or fused with  $R^{64A}$ ;  $R^{64A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{65}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{65A}$ ;  $R^{65A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{66}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{67}$ ,  $OR^{67}$ ,  $SR^{67}$ ,  $S(O)R^{67}$ ,  $SO_2R^{67}$ ,  $C(O)R^{67}$ ,  $CO(O)R^{67}$ ,  $OC(O)R^{67}$ ,  $OC(O)OR^{67}$ ,  $NH_2$ ,  $NHR^{67}$ ,  $N(R^{67})_2$ ,  $NHC(O)R^{67}$ ,  $NR^{67}C(O)R^{67}$ ,  $NHS(O)_2R^{67}$ ,  $NR^{67}S(O)_2R^{67}$ ,  $NHC(O)OR^{67}$ ,  $NR^{67}C(O)OR^{67}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{67}$ ,  $NHC(O)N(R^{67})_2$ ,  $NR^{67}C(O)NHR^{67}$ ,  $NR^{67}C(O)N(R^{67})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{67}$ ,  $C(O)N(R^{67})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{67}$ ,  $C(O)NHSO_2R^{67}$ ,  $C(O)NR^{67}SO_2R^{67}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{67}$ ,  $SO_2N(R^{67})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{67}$ ,  $C(N)N(R^{67})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$  substituents;

$R^{67}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$ ,  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$ , and  $R^{67}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $OR^{68}$ ,  $SR^{68}$ ,  $S(O)R^{68}$ ,  $SO_2R^{68}$ ,  $C(O)R^{68}$ ,  $CO(O)R^{68}$ ,  $OC(O)R^{68}$ ,  $OC(O)OR^{68}$ ,  $NH_2$ ,  $NHR^{68}$ ,  $N(R^{68})_2$ ,  $NHC(O)R^{68}$ ,  $NR^{68}C(O)R^{68}$ ,  $NHS(O)_2R^{68}$ ,  $NR^{68}S(O)_2R^{68}$ ,  $NHC(O)OR^{68}$ ,  $NR^{68}C(O)OR^{68}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{68}$ ,  $NHC(O)N(R^{68})_2$ ,  $NR^{68}C(O)NHR^{68}$ ,  $NR^{68}C(O)N(R^{68})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{68}$ ,  $C(O)N(R^{68})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{68}$ ,  $C(O)NHSO_2R^{68}$ ,  $C(O)NR^{68}SO_2R^{68}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{68}$ ,  $SO_2N(R^{68})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{68}$ ,  $C(N)N(R^{68})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{68}$  is  $R^{69}$ ,  $R^{70}$ ,  $R^{71}$  or  $R^{72}$ ;

$R^{69}$  is phenyl, which is unfused or fused with  $R^{69A}$ ;  $R^{69A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{70}$  is heteroaryl, which is unfused or fused with  $R^{70A}$ ;  $R^{70A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;



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$R^{71}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{71A}$ ;  $R^{71A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{72}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{73}$ ,  $OR^{73}$ ,  $SR^{73}$ ,  $S(O)R^{73}$ ,  $SO_2R^{73}$ ,  $C(O)R^{73}$ ,  $CO(O)R^{73}$ ,  $OC(O)R^{73}$ ,  $OC(O)OR^{73}$ ,  $NH_2$ ,  $NHR^{73}$ ,  $N(R^{73})_2$ ,  $NHC(O)R^{73}$ ,  $NR^{73}C(O)R^{73}$ ,  $NHS(O)_2R^{73}$ ,  $NR^{73}S(O)_2R^{73}$ ,  $NHC(O)OR^{73}$ ,  $NR^{73}C(O)OR^{73}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{73}$ ,  $NHC(O)N(R^{73})_2$ ,  $NR^{73}C(O)NHR^{73}$ ,  $NR^{73}C(O)N(R^{73})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{73}$ ,  $C(O)N(R^{73})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{73}$ ,  $C(O)NHSO_2R^{73}$ ,  $C(O)NR^{73}SO_2R^{73}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{73}$ ,  $SO_2N(R^{73})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{73}$ ,  $C(N)N(R^{73})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{73}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by  $R^{69}$ ,  $R^{70}$ , and  $R^{71}$  are unsubstituted or substituted with one or two or three or four of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $C(O)NHOH$ ,  $SO_2NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ .

Another embodiment of this invention pertains to compounds of Formula (I), wherein

$A^1$  is  $N$  or  $C(A^2)$ ;

$A^2$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ;

$B^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ;

$D^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ;

$E^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC$

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$(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ; and

$Y^1$  is  $H$ ,  $CN$ ,  $NO_2$ ,  $C(O)OH$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ ,  $OCF_2CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $C(O)R^{17}$ ,  $C(O)OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ ,  $NH_2$ ,  $NHR^{17}$ ,  $N(R^{17})_2$ ,  $NHC(O)R^{17}$ ,  $C(O)NHR^{17}$ ,  $C(O)N(R^{17})_2$ ,  $NHS(O)R^{17}$  or  $NHSO_2R^{17}$ ; or

$E^1$  and  $Y^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$A^2$ ,  $B^1$ , and  $D^1$  are independently selected  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ; or

$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$A^2$ ,  $D^1$ , and  $E^1$  are independently selected  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ; or

$A^2$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$D^1$ ,  $E^1$ , and  $Y^1$  are independently selected  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ; or

$A^2$  and  $D^1$ , together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

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B<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNH<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

G<sup>1</sup> is H, or C(O)OR;

R is alkyl;

R<sup>1</sup> is R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup>;

R<sup>1,4</sup> is cycloalkyl, cycloalkenyl or cycloalkynyl;

R<sup>2</sup> is phenyl, which is unfused or fused with R<sup>2,4</sup>; R<sup>2,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>3</sup> is heteroaryl, which is unfused or fused with R<sup>3,4</sup>; R<sup>3,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>4,4</sup>; R<sup>4,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>5</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>6</sup>, NC(R<sup>6A</sup>)(R<sup>6B</sup>), R<sup>7</sup>, OR<sup>7</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, C(O)R<sup>7</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>7</sup>, C(O)N(R<sup>7</sup>)<sub>2</sub>, NHC(O)R<sup>7</sup>, NR<sup>7</sup>C(O)R<sup>7</sup>, NHSO<sub>2</sub>R<sup>7</sup>, NHC(O)OR<sup>7</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>7</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>7</sup>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NHR<sup>7</sup>, OH, (O), C(O)OH, N<sub>3</sub>, CN, NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>6</sup> is C<sub>2</sub>-C<sub>5</sub>-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N<sub>3</sub>, CN, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, NH<sub>2</sub>, NH(CH<sub>3</sub>) or N(CH<sub>3</sub>)<sub>2</sub>;

R<sup>6A</sup> and R<sup>6B</sup> are independently selected alkyl or, together with the N to which they are attached, R<sup>6C</sup>;

R<sup>6C</sup> is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH<sub>2</sub> moiety unreplaced or replaced with O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup>;

R<sup>8</sup> is phenyl, which is unfused or fused with R<sup>8,4</sup>; R<sup>8,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>9</sup> is heteroaryl, which is unfused or fused with R<sup>9,4</sup>; R<sup>9,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>10,4</sup>; R<sup>10,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>11</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup>, SR<sup>12</sup>, S(O)R<sup>12</sup>, SO<sub>2</sub>R<sup>12</sup>, C(O)R<sup>12</sup>, CO(O)R<sup>12</sup>, OC(O)R<sup>12</sup>, OC(O)OR<sup>12</sup>, NH<sub>2</sub>, NHR<sup>12</sup>, N(R<sup>12</sup>)<sub>2</sub>, NHC(O)R<sup>12</sup>, NR<sup>12</sup>C(O)R<sup>12</sup>, NHS(O)<sub>2</sub>R<sup>12</sup>, NR<sup>12</sup>S(O)<sub>2</sub>R<sup>12</sup>, NHC(O)OR<sup>12</sup>, NR<sup>12</sup>C(O)OR<sup>12</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>12</sup>, NHC(O)N(R<sup>12</sup>)<sub>2</sub>, NR<sup>12</sup>C(O)NHR<sup>12</sup>, NR<sup>12</sup>C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>12</sup>, C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHNH<sub>2</sub>, C(O)NHSO<sub>2</sub>R<sup>12</sup>, C(O)NR<sup>12</sup>SO<sub>2</sub>R<sup>12</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>12</sup>, SO<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>12</sup>, C(N)N(R<sup>12</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

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R<sup>12</sup> is R<sup>13</sup>; R<sup>14</sup>; R<sup>15</sup> or R<sup>16</sup>;

R<sup>13</sup> is phenyl, which is unfused or fused with R<sup>13,4</sup>; R<sup>13,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>14</sup> is heteroaryl, which is unfused or fused with R<sup>14,4</sup>; R<sup>14,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>15</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R<sup>15,4</sup>; R<sup>15,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>16</sup> is alkyl, alkenyl or alkynyl;

R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> or R<sup>21</sup>;

R<sup>18</sup> is phenyl, which is unfused or fused with R<sup>18,4</sup>; R<sup>18,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>19</sup> is heteroaryl, which is unfused or fused with R<sup>19,4</sup>; R<sup>19,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>20</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R<sup>20,4</sup>; R<sup>20,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>21</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, OR<sup>22</sup>, SR<sup>22</sup>, S(O)R<sup>22</sup>, SO<sub>2</sub>R<sup>22</sup>, C(O)R<sup>22</sup>, CO(O)R<sup>22</sup>, OC(O)R<sup>22</sup>, OC(O)OR<sup>22</sup>, NH<sub>2</sub>, NHR<sup>22</sup>, N(R<sup>22</sup>)<sub>2</sub>, NHC(O)R<sup>22</sup>, NR<sup>22</sup>C(O)R<sup>22</sup>, NHS(O)<sub>2</sub>R<sup>22</sup>, NR<sup>22</sup>S(O)<sub>2</sub>R<sup>22</sup>, NHC(O)OR<sup>22</sup>, NR<sup>22</sup>C(O)OR<sup>22</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>22</sup>, NHC(O)N(R<sup>22</sup>)<sub>2</sub>, NR<sup>22</sup>C(O)NHR<sup>22</sup>, NR<sup>22</sup>C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>22</sup>, C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHNH<sub>2</sub>, C(O)NHSO<sub>2</sub>R<sup>22</sup>, C(O)NR<sup>22</sup>SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>22</sup>, SO<sub>2</sub>N(R<sup>22</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>22</sup>, C(N)N(R<sup>22</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>23</sup>, R<sup>24</sup> or R<sup>25</sup>;

R<sup>23</sup> is phenyl, which is unfused or fused with R<sup>23,4</sup>; R<sup>23,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>24,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>25</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>25,4</sup>; R<sup>25,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z<sup>1</sup> is R<sup>26</sup> or R<sup>27</sup>;

Z<sup>2</sup> is R<sup>28</sup>, R<sup>29</sup> or R<sup>30</sup>;

Z<sup>1,4</sup> and Z<sup>2,4</sup> are both absent or are taken together to form CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub> or Z<sup>12,4</sup>;

Z<sup>12,4</sup> is C<sub>2</sub>-C<sub>6</sub>-alkylene having one or two CH<sub>2</sub> moieties replaced by NH, N(CH<sub>3</sub>), S, S(O) or SO<sub>2</sub>;

L<sup>1</sup> is a R<sup>37</sup>, OR<sup>37</sup>, SR<sup>37</sup>, S(O)R<sup>37</sup>, SO<sub>2</sub>R<sup>37</sup>, C(O)R<sup>37</sup>, CO(O)R<sup>37</sup>, OC(O)R<sup>37</sup>, OC(O)OR<sup>37</sup>, NHR<sup>37</sup>, C(O)NH, C(O)NR<sup>37</sup>, C(O)NHNH<sub>2</sub>, C(O)NHSO<sub>2</sub>R<sup>37</sup>, SO<sub>2</sub>NH, SO<sub>2</sub>NHR<sup>37</sup>, C(N)NH, C(N)NHR<sup>37</sup>;

R<sup>26</sup> is phenylene, which is unfused or fused with R<sup>26,4</sup>; R<sup>26,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>27</sup> is heteroarylene, which is unfused or fused with R<sup>27,4</sup>; R<sup>27,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>28</sup> is phenylene, which is unfused or fused with R<sup>28,4</sup>; R<sup>28,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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$R^{29}$  is heteroarylene, which is unfused or fused with  $R^{29A}$ ;  $R^{29A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{30}$  is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with  $R^{30A}$ ;  $R^{30A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{37}$  is a bond or  $R^{37A}$ ;

$R^{37A}$  is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected  $R^{37B}$ ,  $OR^{37B}$ ,  $SR^{37B}$ ,  $S(O)R^{37B}$ ,  $SO_2R^{37B}$ ,  $C(O)R^{37B}$ ,  $CO(O)R^{37B}$ ,  $OC(O)R^{37B}$ ,  $OC(O)OR^{37B}$ ,  $NH_2$ ,  $NHR^{37B}$ ,  $N(R^{37B})_2$ ,  $NHC(O)R^{37B}$ ,  $NR^{37B}C(O)R^{37B}$ ,  $NHS(O)_2R^{37B}$ ,  $NR^{37B}S(O)_2R^{37B}$ ,  $NHC(O)OR^{37B}$ ,  $NR^{37B}C(O)OR^{37B}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{37B}$ ,  $NHC(O)N(R^{37B})_2$ ,  $NR^{37B}C(O)NHR^{37B}$ ,  $NR^{37B}C(O)N(R^{37B})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{37B}$ ,  $C(O)N(R^{37B})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{37B}$ ,  $C(O)NHSO_2R^{37B}$ ,  $C(O)NR^{37B}SO_2R^{37B}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{37B}$ ,  $SO_2N(R^{37B})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{37B}$ ,  $C(N)N(R^{37B})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  and  $I$  substituents;  $R^{37B}$  is alkyl, alkenyl, alkynyl, or  $R^{37C}$ ;

$R^{37C}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

$Z^3$  is  $R^{38}$ ,  $R^{39}$  or  $R^{40}$ ;

$R^{38}$  is phenyl, which is unfused or fused with  $R^{38A}$ ;  $R^{38A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{39}$  is heteroaryl, which is unfused or fused with  $R^{39A}$ ;  $R^{39A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{40}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{40A}$ ;  $R^{40A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by  $R^{26}$  and  $R^{27}$  are substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are absent) or further substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are present) with  $R^{41}$ ,  $OR^{41}$ ,  $SR^{41}$ ,  $S(O)R^{41}$ ,  $SO_2R^{41}$ ,  $C(O)R^{41}$ ,  $CO(O)R^{41}$ ,  $OC(O)R^{41}$ ,  $OC(O)OR^{41}$ ,  $NHR^{41}$ ,  $N(R^{41})_2$ ,  $NHC(O)R^{41}$ ,  $NR^{41}C(O)R^{41}$ ,  $NHS(O)_2R^{41}$ ,  $NR^{41}S(O)_2R^{41}$ ,  $NHC(O)OR^{41}$ ,  $NR^{41}C(O)OR^{41}$ ,  $NHC(O)NHR^{41}$ ,  $NHC(O)N(R^{41})_2$ ,  $NR^{41}C(O)NHR^{41}$ ,  $NR^{41}C(O)N(R^{41})_2$ ,  $C(O)NHR^{41}$ ,  $C(O)N(R^{41})_2$ ,  $C(O)NHOH$ ,  $C(O)NHSO_2R^{41}$ ,  $C(O)NR^{41}SO_2R^{41}$ ,  $SO_2NHR^{41}$ ,  $SO_2N(R^{41})_2$ ,  $C(N)NHR^{41}$ , or  $C(N)N(R^{41})_2$ ;

$R^{41}$  is heteroaryl, which is fused with  $R^{43A}$ ;  $R^{43A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is fused with benzene, heteroarene or  $R^{43B}$ ;  $R^{43B}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by  $E^1$  and  $Y^1$  together,  $Y^1$  and  $B^1$  together,  $A^2$  and  $B^1$  together,  $A^2$  and  $D^1$  together,  $R^{1A}$ ,  $R^2$ ,  $R^{2A}$ ,  $R^3$ ,  $R^{3A}$ ,  $R^4$ ,  $R^{4A}$ ,  $R^6$ ,  $R^{6C}$ ,  $R^8$ ,  $R^{8A}$ ,  $R^9$ ,  $R^{9A}$ ,  $R^{10}$ ,  $R^{10A}$ ,  $R^{13}$ ,  $R^{13A}$ ,  $R^{14}$ ,  $R^{14A}$ ,  $R^{15}$ ,  $R^{15A}$ ,  $R^{18}$ ,  $R^{18A}$ ,  $R^{19}$ ,  $R^{19A}$ ,  $R^{20}$ ,  $R^{20A}$ ,  $R^{23}$ ,  $R^{23A}$ ,  $R^{24}$ ,  $R^{24A}$ ,  $R^{25}$ ,  $R^{25A}$ ,  $R^{26}$ ,  $R^{26A}$ ,  $R^{27}$ ,  $R^{27A}$ ,  $R^{28}$ ,  $R^{28A}$ ,  $R^{29}$ ,  $R^{29A}$ ,  $R^{30}$ ,  $R^{30A}$ ,  $R^{37B}$ ,  $R^{38}$ ,  $R^{38A}$ ,  $R^{39}$ ,  $R^{39A}$ ,  $R^{40}$ , and  $R^{40A}$  are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SR^{57}$ ,  $S(O)R^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $OC(O)R^{57}$ ,  $OC(O)OR^{57}$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NR^{57}C(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $NR^{57}S(O)_2R^{57}$ ,  $NHC(O)OR^{57}$ ,  $NR^{57}C(O)OR^{57}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{57}$ ,  $NHC(O)N(R^{57})_2$ ,  $NR^{57}C(O)NHR^{57}$ ,  $NR^{57}C(O)N(R^{57})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{57}$ ,  $C(O)N(R^{57})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{57}$ ,  $C(O)NHSO_2R^{57}$ ,  $C(O)NR^{57}SO_2R^{57}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{57}$ ,  $SO_2N(R^{57})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)$

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$NH_2$ ,  $C(N)NHR^{57}$ ,  $C(N)N(R^{57})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl, which is unfused or fused with  $R^{58A}$ ;  $R^{58A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{59}$  is heteroaryl, which is unfused or fused with  $R^{59A}$ ;  $R^{59A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{60}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{60A}$ ;  $R^{60A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{61}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $SR^{62}$ ,  $S(O)R^{62}$ ,  $SO_2R^{62}$ ,  $C(O)R^{62}$ ,  $CO(O)R^{62}$ ,  $OC(O)R^{62}$ ,  $OC(O)OR^{62}$ ,  $NH_2$ ,  $NHR^{62}$ ,  $N(R^{62})_2$ ,  $NHC(O)R^{62}$ ,  $NR^{62}C(O)R^{62}$ ,  $NHS(O)_2R^{62}$ ,  $NR^{62}S(O)_2R^{62}$ ,  $NHC(O)OR^{62}$ ,  $NR^{62}C(O)OR^{62}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{62}$ ,  $NHC(O)N(R^{62})_2$ ,  $NR^{62}C(O)NHR^{62}$ ,  $NR^{62}C(O)N(R^{62})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{62}$ ,  $C(O)N(R^{62})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{62}$ ,  $C(O)NHSO_2R^{62}$ ,  $C(O)NR^{62}SO_2R^{62}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{62}$ ,  $SO_2N(R^{62})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{62}$ ,  $C(N)N(R^{62})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{62}$  is  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$  or  $R^{66}$ ;

$R^{63}$  is phenyl, which is unfused or fused with  $R^{63A}$ ;  $R^{63A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{64}$  is heteroaryl, which is unfused or fused with  $R^{64A}$ ;  $R^{64A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{65}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with  $R^{65A}$ ;  $R^{65A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{66}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{67}$ ,  $OR^{67}$ ,  $SR^{67}$ ,  $S(O)R^{67}$ ,  $SO_2R^{67}$ ,  $C(O)R^{67}$ ,  $CO(O)R^{67}$ ,  $OC(O)R^{67}$ ,  $OC(O)OR^{67}$ ,  $NH_2$ ,  $NHR^{67}$ ,  $N(R^{67})_2$ ,  $NHC(O)R^{67}$ ,  $NR^{67}C(O)R^{67}$ ,  $NHS(O)_2R^{67}$ ,  $NR^{67}S(O)_2R^{67}$ ,  $NHC(O)OR^{67}$ ,  $NR^{67}C(O)OR^{67}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{67}$ ,  $NHC(O)N(R^{67})_2$ ,  $NR^{67}C(O)NHR^{67}$ ,  $NR^{67}C(O)N(R^{67})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{67}$ ,  $C(O)N(R^{67})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{67}$ ,  $C(O)NHSO_2R^{67}$ ,  $C(O)NR^{67}SO_2R^{67}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{67}$ ,  $SO_2N(R^{67})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{67}$ ,  $C(N)N(R^{67})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$  substituents;

$R^{67}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$ ,  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$ , and  $R^{67}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $OR^{68}$ ,  $SR^{68}$ ,  $S(O)R^{68}$ ,  $SO_2R^{68}$ ,  $C(O)R^{68}$ ,  $CO(O)R^{68}$ ,  $OC(O)R^{68}$ ,  $OC(O)OR^{68}$ ,  $NH_2$ ,  $NHR^{68}$ ,  $N(R^{68})_2$ ,  $NHC(O)R^{68}$ ,  $NR^{68}C(O)R^{68}$ ,  $NHS(O)_2R^{68}$ ,  $NR^{68}S(O)_2R^{68}$ ,  $NHC(O)OR^{68}$ ,  $NR^{68}C(O)OR^{68}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{68}$ ,  $NHC(O)N(R^{68})_2$ ,  $NR^{68}C(O)NHR^{68}$ ,  $NR^{68}C(O)N(R^{68})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{68}$ ,  $C(O)N(R^{68})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{68}$ ,  $C(O)NR^{68}SO_2R^{68}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{68}$ ,  $SO_2N(R^{68})_2$ ,  $C(O)$



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H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>68</sup>, C(N)N(R<sup>68</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>68</sup> is R<sup>69</sup>, R<sup>79</sup>, R<sup>71</sup> or R<sup>72</sup>;

R<sup>69</sup> is phenyl, which is unfused or fused with R<sup>69A</sup>; R<sup>69A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>70</sup> is heteroaryl, which is unfused or fused with R<sup>70A</sup>; R<sup>70A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>71</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>71A</sup>; R<sup>71A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>72</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>73</sup>, OR<sup>73</sup>, SR<sup>73</sup>, S(O)R<sup>73</sup>, SO<sub>2</sub>R<sup>73</sup>, C(O)R<sup>73</sup>, CO(O)R<sup>73</sup>, OC(O)R<sup>73</sup>, OC(O)OR<sup>73</sup>, NH<sub>2</sub>, NHR<sup>73</sup>, N(R<sup>73</sup>)<sub>2</sub>, NHC(O)R<sup>73</sup>, NR<sup>73</sup>C(O)R<sup>73</sup>, NHS(O)<sub>2</sub>R<sup>73</sup>, NR<sup>73</sup>S(O)<sub>2</sub>R<sup>73</sup>, NHC(O)OR<sup>73</sup>, NR<sup>73</sup>C(O)OR<sup>73</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>73</sup>, NHC(O)N(R<sup>73</sup>)<sub>2</sub>, NR<sup>73</sup>C(O)NHR<sup>73</sup>, NR<sup>73</sup>C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>73</sup>, C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>73</sup>, C(O)NHSO<sub>2</sub>R<sup>73</sup>, C(O)NR<sup>73</sup>SO<sub>2</sub>R<sup>73</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>73</sup>, SO<sub>2</sub>N(R<sup>73</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>73</sup>, C(N)N(R<sup>73</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>73</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R<sup>69</sup>, R<sup>70</sup>, and R<sup>71</sup> are unsubstituted or substituted with one or two or three or four of independently selected NH<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I.

In one embodiment of Formula (I), A<sup>1</sup> is N, and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>) and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H, F, Cl, Br, or I; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and G<sup>1</sup> is H.

In one embodiment of Formula (I), B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>, and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>, and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; and G<sup>1</sup> is H.

In one embodiment of Formula (I), D<sup>1</sup> is H or Cl. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment

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of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H.

In one embodiment of Formula (I), E<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; D<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; D<sup>1</sup> is Cl, and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H.

In one embodiment of Formula (I), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (I), Y<sup>1</sup> is H. In another embodiment of Formula (I), Y<sup>1</sup> is CN. In another embodiment of Formula (I), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (I), Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (I), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (I), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (I), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (I), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (I), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); and A<sup>2</sup> is H. In another embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>.

In one embodiment of Formula (I), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (I), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (I), R<sup>1</sup>

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is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>; R<sup>60</sup> is heterocycloalkyl; and R<sup>61</sup> is alkyl. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and

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the alkyl is methyl. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.

In one embodiment of Formula (I), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted with R<sup>7</sup>, OR<sup>7</sup>, OH, CN, or F. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is substituted with R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, or N(R<sup>7</sup>)<sub>2</sub>.

In one embodiment of Formula (I), R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup> which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>7</sup> is R<sup>8</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>7</sup> is R<sup>9</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>7</sup> is R<sup>10</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>7</sup> is R<sup>11</sup> which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (I), R<sup>8</sup> is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (I), R<sup>9</sup> is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>9</sup> is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>9</sup> is furanyl; which is unsubstituted.

In one embodiment of Formula (I), R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>10</sup> is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>10</sup> is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>10</sup> is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>10</sup> is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>10</sup> is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>10</sup> is heterocycloalkyl which is fused with R<sup>10,4</sup>; and R<sup>10,4</sup> is heteroarene. In another embodiment of Formula (I), R<sup>10</sup> is 5,6,7,8-tetrahydroimidazo [1,2-a]pyridinyl.

In one embodiment of Formula (I), R<sup>11</sup> is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>11</sup> is alkyl. In another embodiment of Formula (I), R<sup>11</sup> is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>11</sup> is alkyl; which is substituted as defined herein. In another embodiment of Formula (I), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>, OR<sup>12</sup>, or CF<sub>3</sub>. In another embodiment of Formula (I), R<sup>11</sup> is alkyl; which is substituted with OR<sup>12</sup>, R<sup>12</sup> is R<sup>16</sup>; and R<sup>16</sup> is alkyl. In another embodiment of Formula (I), R<sup>11</sup> is alkyl; which is substituted with CF<sub>3</sub>. In another embodiment of Formula (I), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>; R<sup>12</sup> is R<sup>14</sup>; and R<sup>14</sup> is heteroaryl.

In one embodiment of Formula (I), A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, F, Br, I, or Cl;

B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Br, I or Cl;

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D<sup>1</sup> is H, F, Br, I, or Cl;  
 E<sup>1</sup> is H; and  
 Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>; or  
 Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and  
 A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H;  
 G<sup>1</sup> is H, or C(O)OR;  
 R is alkyl;  
 R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>;  
 R<sup>4</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>5</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, CN, OH, F, Cl, Br or I;  
 R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, or R<sup>11</sup>;  
 R<sup>8</sup> is phenyl;  
 R<sup>9</sup> is heteroaryl;  
 R<sup>10</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R<sup>10A</sup>, R<sup>10A</sup> is heteroarene;  
 R<sup>11</sup> is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup> or CF<sub>3</sub>;  
 R<sup>12</sup> is R<sup>14</sup> or R<sup>16</sup>;  
 R<sup>14</sup> is heteroaryl;  
 R<sup>16</sup> is alkyl;  
 R<sup>17</sup> is R<sup>21</sup>;  
 R<sup>21</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, F, Cl, Br or I;  
 R<sup>22</sup> is R<sup>25</sup>;  
 R<sup>25</sup> is heterocycloalkyl;  
 Z<sup>1</sup> is R<sup>26</sup>;  
 Z<sup>2</sup> is R<sup>30</sup>;  
 Z<sup>1A</sup> and Z<sup>2A</sup> are both absent;  
 L<sup>1</sup> is a R<sup>37</sup>;  
 R<sup>26</sup> is phenylene;  
 R<sup>30</sup> is heterocycloalkylene;  
 R<sup>37</sup> is R<sup>37A</sup>;  
 R<sup>37A</sup> is alkylene;  
 Z<sup>3</sup> is R<sup>38</sup>, or R<sup>40</sup>;  
 R<sup>38</sup> is phenyl;  
 R<sup>40</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkenyl;  
 wherein the moiety represented by R<sup>26</sup> is substituted with OR<sup>41</sup>;  
 R<sup>41</sup> is heteroaryl, which is fused with R<sup>43A</sup>; R<sup>43A</sup> is heteroarene; which is unfused or fused with benzene;  
 wherein the cyclic moieties represented by Y<sup>1</sup> and B<sup>1</sup> together, R<sup>4</sup>, R<sup>8</sup>, R<sup>10</sup>, R<sup>25</sup>, R<sup>30</sup>, R<sup>38</sup>, and R<sup>40</sup> are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NHS(O)<sub>2</sub>R<sup>57</sup>, OH, CN, (O), F, Cl, Br or I;  
 R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;  
 R<sup>57</sup> is R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup> or R<sup>61</sup>;  
 R<sup>58</sup> is phenyl;  
 R<sup>59</sup> is heteroaryl;  
 R<sup>60</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>61</sup> is alkyl which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, C(O)OH, CN, F, Cl, Br or I;  
 R<sup>62</sup> is R<sup>65</sup>, or R<sup>66</sup>;  
 R<sup>65</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>66</sup> is alkyl which is unsubstituted or substituted with OR<sup>67</sup>;  
 R<sup>67</sup> is alkyl;

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wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, and R<sup>60</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, F, Cl, Br or I;  
 R<sup>68</sup> is R<sup>71</sup> or R<sup>72</sup>;  
 R<sup>71</sup> is heterocycloalkyl; and  
 R<sup>72</sup> is alkyl, which is unsubstituted or substituted with one or two F.  
 Still another embodiment pertains to compounds having Formula (I), which are  
 4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 2-(9H-carbazol-4-yloxy)-4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)benzamide;  
 2-(9H-carbazol-4-yloxy)-4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl)sulfonyl)benzamide;  
 Trans-4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(4-morpholin-4-yl)cyclohexyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(1,4-dioxan-2-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tet-



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rahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-ylmethoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-({3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl)sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl)sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-(trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-(trifluoromethyl)sulfonyl)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;

N-({5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-acetyl)pyridin-4-yl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-



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dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl)sulfonyl]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(2-methoxyethoxy)ethyl)sulfonyl]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-N-({4-[(4-bis(cyclopropylmethyl)amino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 10 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 15 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 20 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 25 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 tert-butyl 3-({4-[(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl)morpholine-4-carboxylate;  
 35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(morpholin-3-ylmethoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 40 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(1-methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 45 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 50 N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({3-nitro-4-[(1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 55 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 60 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-({5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 65 N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-

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dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-morpholin-4-yl)cyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-yl]piperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1,1-dioxidothiomorpholin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[1-(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-[(4-morpholin-4-yl)cyclohexyl]amino]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;  
2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;  
Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-N-[(5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl]-2-nitrophenoxymethyl)-4-fluoropiperidine-1-carboxylate;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cyclohexyl}amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(2-methoxyethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclobutylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyr-

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rolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(methylsulfonyl)piperidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(1-acetyl)piperidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(methylsulfonyl)pyrrolidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1R,3R)-3-hydroxycyclopentyl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1S,3S)-3-hydroxycyclopentyl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1S,3R)-3-hydroxycyclopentyl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1R,3S)-3-hydroxycyclopentyl]methyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-cyclopropylpiperidin-4-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(2-fluoroethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(2,2-difluoroethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(2,2-difluoroethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(2,2-difluoroethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-{[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(2,2-difluoroethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-methoxybenzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-methoxybenzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(difluoromethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-([4-([4-(acetylamino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(hydroxybenzyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(difluoromethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(methylsulfonyl)amino]cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-cyclopropylpiperidin-4-yl]amino)-3-(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([1-oxetan-3-ylpi-

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peridin-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(2-morpholin-4-ylethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

(2-{[4-({4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)amino}methyl)morpholin-4-yl)acetic acid;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(4-cyclopropyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

ethyl 4-(4-{[4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-{(trifluoromethyl)sulfonyl}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[1-isopropylpiperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[1-(tert-butyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[1-(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-{(trifluoromethyl)sulfonyl}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro- $\lambda^6$ -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-methoxytetrahydro-2H-pyran-4-yl]methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-{(3R)-tetrahydrofuran-3-ylamino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[1-(tert-butyl)piperidin-4-yl]amino}-3-{(trifluoromethyl)sulfonyl}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-{(trifluoromethyl)sulfonyl}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[1-(cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[4-(fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[4-(fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-(3R)-1-[2-(2-methoxy-

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ethoxyethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-[(5-chloro-6-{[4-fluorotetrahydro-2H-pyran-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-[(3-nitro-4-{[tetrahydro-2H-pyran-4-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[tetrahydro-2H-pyran-4-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[tetrahydro-2H-pyran-4-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[tetrahydro-2H-pyran-4-ylmethoxy]pyridin-3-yl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[4-fluoro-1-methylpiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-[(3-nitro-4-{[tetrahydro-2H-pyran-4-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-[(5-chloro-6-{[4-fluorotetrahydro-2H-pyran-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[(4-{[tetrahydro-2H-pyran-4-ylmethyl]amino}-3-(trifluoromethyl)phenyl)sulfonyl]benzamide;  
 N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[tetrahydro-2H-pyran-4-yl]ethoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-furylmethoxy]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[4-fluoro-1-methylpiperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[tetrahydro-2H-pyran-4-ylmethoxy]phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlo-

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rophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({[5-chloro-6-(2-methoxyethoxy)pyridin-3-yl}sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[5-fluoro-6-(tetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({[3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy]phenyl}sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({[3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy]phenyl}sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl]piperidin-1-yl)-N-({[3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({[6-(tetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)benzamide;

N-({5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[6-(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[6-(cis-4-methoxycyclo-

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hexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({[3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy]phenyl}sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[4-{[3-(cyclopropyl(1,3-thiazol-5-yl)methyl]amino]propyl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({[3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[3-chloro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[4-{[3-(cyclopropyl(2,2,2-trifluoroethyl)amino]propyl]amino)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({[3-chloro-4-{[1-(oxetan-3-yl)piperidin-4-yl]methoxy]phenyl}sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[4-{[3-(cyclopropyl(oxetan-3-yl)amino]propyl]amino)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({[3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy]phenyl}sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({[3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({[5-chloro-6-[(2S)-4-cyclopropylmorpholin-2-yl]methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperidin-1-yl)-N-({[3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperidin-1-yl)-N-({[3-chloro-4-(tetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

methyl 2-({[4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo



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[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)amino)methyl]morpholine-4-carboxylate;  
 2-[[4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)amino)methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([4-(methylsulfonyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([3-(cyclobutyl(cyclopropyl)amino)propyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(trans-4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl]-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azapirrol[5.5]undec-8-en-8-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl]piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([4-cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl]piperazin-1-yl)-N-([4-([[(4-cyclopropylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([4-cyclopropylmorpholin-2-yl)methyl]amino]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 2-[[2-chloro-4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyr-

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rolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]phenyl)amino)methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;  
 (2S)-2-[[3-chloro-5-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;  
 N-[(5-chloro-6-([4-cyclopropylmorpholin-2-yl)methyl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 2-[[3-chloro-5-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-([1R,2R,4R,5R]-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([4-([2-cyanoethyl](cyclopropyl)amino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-([1R,2S,4R,5R]-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([4-([4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[2-(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-{[5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-{[5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-{[5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-cyano-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl]amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-{[3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[2-(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl]methoxy}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-nitro-6-[(tetrahydro-2H-

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pyran-4-ylmethyl)amino]pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-cyano-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 {[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]}{4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl}amino}methyl pivalate;  
 {[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]}{4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl}amino}methyl butyrate;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]}{4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl}amino}methyl  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl}benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-5-nitropyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy]pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-(methoxymethyl)cyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-[(1-(1,3-thiazol-2-yl)piperidin-4-yl)methoxy]pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-5-nitropyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.  
 Still another embodiment pertains to 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.  
 Still another embodiment pertains to Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-morpholin-4-ylcyclo-

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hexyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

Still another embodiment pertains to Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

Still another embodiment pertains to Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

Still another embodiment pertains to 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

Another embodiment pertains to the compound N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(<sup>2</sup>H<sub>8</sub>)piperazin-1-yl]-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-[(5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-py-

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ran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-cyclopropyl(oxetan-3-yl)amino]propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-cyclopropyl(oxetan-3-yl)amino]propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-cyclopropyl(oxetan-3-yl)amino]propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxan-2-yl)methoxy]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;





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D<sup>1</sup> is Cl. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

In one embodiment of Formula (II), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (II), Y<sup>1</sup> is H. In another embodiment of Formula (II), Y<sup>1</sup> is CN. In another embodiment of Formula (II), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (II), Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (II), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (II), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (II), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (II), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (II), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (II), Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); and A<sup>2</sup> is H. In another embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; and D<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; D<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; D<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>.

In one embodiment of Formula (II), Y<sup>1</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (II), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

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In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>; R<sup>60</sup> is heterocycloalkyl; and R<sup>61</sup> is alkyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is tetrahydropyranlyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.



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In one embodiment of Formula (II),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is unsubstituted or substituted. In one embodiment of Formula (II),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is unsubstituted or substituted with  $R^7$ ,  $OR^7$ ,  $OH$ ,  $CN$ , or  $F$ . In another embodiment of Formula (II),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is substituted with  $R^7$ ,  $OR^7$ ,  $NHR^7$ , or  $N(R^7)_2$ .

In one embodiment of Formula (II),  $R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$  or  $R^{11}$  which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^7$  is  $R^8$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^7$  is  $R^9$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^7$  is  $R^{10}$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^7$  is  $R^{11}$  which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (II),  $R^8$  is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (II),  $R^9$  is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^9$  is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^9$  is furanyl; which is unsubstituted.

In one embodiment of Formula (II),  $R^{10}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{10}$  is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{10}$  is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{10}$  is tetrahydropyranyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{10}$  is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{10}$  is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{10}$  is heterocycloalkyl which is fused with  $R^{10A}$ ; and  $R^{10A}$  is heteroarene. In another embodiment of Formula (II),  $R^{10}$  is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (II),  $R^{11}$  is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{11}$  is alkyl. In another embodiment of Formula (II),  $R^{11}$  is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ,  $OR^{12}$ , or  $CF_3$ . In another embodiment of Formula (II),  $R^{11}$  is alkyl; which is substituted with  $OR^{12}$ ;  $R^{12}$  is  $R^{16}$ ; and  $R^{16}$  is alkyl. In another embodiment of Formula (II),  $R^{11}$  is alkyl; which is substituted with  $CF_3$ . In another embodiment of Formula (II),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ,  $R^{12}$  is  $R^{14}$ , and  $R^{14}$  is heteroaryl.

In one embodiment of Formula (II),

$n$  is 0;

$A^1$  is  $N$  or  $C(A^2)$ ;

$A^2$  is  $H$ ,  $F$ ,  $Br$ ,  $I$ , or  $Cl$ ;

$B^1$  is  $R^1$ ,  $OR^1$ ,  $NHR^1$ ,  $NHC(O)R^1$ ,  $F$ ,  $Br$ ,  $I$  or  $Cl$ ;

$D^1$  is  $H$ ,  $F$ ,  $Br$ ,  $I$ , or  $Cl$ ;

$E^1$  is  $H$ ; and

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$Y^1$  is  $H$ ,  $CN$ ,  $NO_2$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ , or  $C(O)NH_2$ ; or

$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and  $A^2$ ,  $D^1$ , and  $E^1$  are independently selected  $H$ ;

$R^1$  is  $R^4$  or  $R^5$ ;

$R^4$  is cycloalkyl, or heterocycloalkyl;

$R^5$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^7$ ,  $OR^7$ ,  $NHR^7$ ,  $N(R^7)_2$ ,  $CN$ ,  $OH$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$ , or  $R^{11}$ ;

$R^8$  is phenyl;

$R^9$  is heteroaryl;

$R^{10}$  is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with  $R^{10A}$ ,  $R^{10A}$  is heteroarene;

$R^{11}$  is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{12}$ ,  $OR^{12}$  or  $CF_3$ ;

$R^{12}$  is  $R^{14}$  or  $R^{16}$ ;

$R^{14}$  is heteroaryl;

$R^{16}$  is alkyl;

$R^{17}$  is  $R^{21}$ ;

$R^{21}$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{22}$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{22}$  is  $R^{25}$ ;

$R^{25}$  is heterocycloalkyl;

$Z^2$  is  $R^{30}$ ;

$Z^{1A}$  and  $Z^{2A}$  are both absent;

$L^1$  is a  $R^{37}$ ;

$R^{30}$  is heterocycloalkylene;

$R^{37}$  is  $R^{37A}$ ;

$R^{37A}$  is alkylene;

$Z^3$  is  $R^{38}$ , or  $R^{40}$ ;

$R^{38}$  is phenyl;

$R^{40}$  is cycloalkyl, cycloalkenyl, or heterocycloalkenyl;

wherein the cyclic moieties represented by  $Y^1$  and  $B^1$  together,  $R^4$ ,  $R^8$ ,  $R^{10}$ ,  $R^{25}$ ,  $R^{30}$ ,  $R^{38}$ , and  $R^{40}$  are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $C(O)N(R^{57})_2$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $OH$ ,  $CN$ ,  $(O)$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl;

$R^{60}$  is cycloalkyl, or heterocycloalkyl;

$R^{61}$  is alkyl which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $N(R^{62})_2$ ,  $C(O)OH$ ,  $CN$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{62}$  is  $R^{65}$ , or  $R^{66}$ ;

$R^{65}$  is cycloalkyl, or heterocycloalkyl;

$R^{66}$  is alkyl which is unsubstituted or substituted with  $OR^{67}$ ;

$R^{67}$  is alkyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ , and  $R^{60}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{68}$  is  $R^{71}$  or  $R^{72}$ ;

$R^{71}$  is heterocycloalkyl; and

$R^{72}$  is alkyl, which is unsubstituted or substituted with one or two  $F$ .

Still another embodiment pertains to compounds having Formula (II), which are

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4-4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl]-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-yl-methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-[(3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {4-[(2S)-1,4-dioxan-2-yl-methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {4-[(2R)-1,4-dioxan-2-yl-methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-( {4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-( {[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-( {4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-( {[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-( {3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-yl-methoxy)phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-( {[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-( {[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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pyridin-5-yloxy)-N-([4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-(trifluoromethyl)phenyl)sulfonyl]benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([4-((tetrahydro-2H-pyran-4-ylmethyl)amino)-3-(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide;  
 Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-([4-((4-morpholin-4-ylcyclohexyl)amino)-3-(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-([4-((1-methylpiperidin-4-yl)amino)-3-(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl]-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;  
 N-([5-bromo-6-((1-methylpiperidin-4-yl)methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-((1-methylpiperidin-4-yl)methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-((2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-5-cyano-4-((tetrahydro-2H-pyran-4-yl)methyl)amino]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([4-((1-acetyl)piperidin-4-yl)amino]-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([2-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-((3-morpholin-4-ylpropyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-([3-chloro-4-([2-(2-methoxyethoxy)ethyl)sulfonyl]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([2-(2-methoxyethoxy)ethyl)sulfonyl]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-((4-morpholin-4-ylcyclohexyl)oxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-bromo-6-((1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl)amino]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-((2-cyanoethyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-([4-((4-morpholin-4-ylcyclohexyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 25 Trans-N-([4-([4-bis(cyclopropylmethyl)amino]cyclohexyl)amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-((1-methylpiperidin-4-yl)methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-((morpholin-3-yl)methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 50 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-([4-((4-morpholin-4-ylcyclohexyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-([4-([4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-([4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 65 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-([4-([4-methoxycyclohexyl)



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methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 3-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl}morpholine-4-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(morpholin-3-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-({[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts, and metabolites thereof.

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1-(2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1-(morpholin-4-yl)cyclohexyl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-({[4-aminotetrahydro-2H-pyran-4-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-morpholin-4-yl)cyclohexyl]amino}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1S,3R]-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1R,3S]-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1-cis-3-fluorotetrahy-



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dro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl] sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl] sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(cyclopropylamino)cyclohexyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl] sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy] pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl]-4-fluoropiperidine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-ylpiperazin-1-yl)cyclohexyl] amino}phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-({[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl) sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([3-nitro-4-([1-oxetan-3-yl]piperidin-4-yl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[1-(cyclobutyl)piperidin-4-yl]amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl) sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([3-nitro-4-([1-tetrahydrofuran-3-yl]piperidin-4-yl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-({[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino}phenyl] sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl}piperazin-1-yl)-N-([4-([3-hydroxy-2,2-dimethyl-



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cyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(3-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-3-morpholin-4-ylcyclopentyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-[(methylsulfonyl)amino]cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-ylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-oxetan-

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3-ylpyrrolidin-3-yl)methyl]amino)phenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(4-[3-(dimethylamino)propoxy]benzyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(4-(2-morpholin-4-ylethoxy)benzyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(4-hydroxy-1-adamantyl)methyl]amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(Z)-4-hydroxy-1-adamantyl)methyl]amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(1R,4R,5R,6S)-5,6-dihydrobicyclo[2.2.1]hept-2-yl)methoxy]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(1R,4R,5S,6R)-5,6-dihydrobicyclo[2.2.1]hept-2-yl)methoxy]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl)methyl]piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({3-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl)methyl]amino)phenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dim-



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ethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-yl]pyrrolidin-3-yl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-{2-(2-methoxyethoxy)ethyl}morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(cyanomethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

(2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfonyl}-2-nitrophenyl)amino]methyl}morpholin-4-yl)acetic acid;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-{[4-(oxetan-3-yl)morpholin-2-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-yl)methoxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfonyl}-2-nitrophenyl)piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-

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dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2-methoxyethyl)piperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(cyanomethyl)piperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfonyl}-2-nitrophenyl)amino]piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro- $\lambda^6$ -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(oxetan-3-yl)morpholin-2-yl)methyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-4-(N,N-dimeth-

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ylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}-3-(trifluoromethyl)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlo-

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rophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([4-({[(trans-4-cyano cyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl] methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoro ethyl)pyrrolidin-3-yl] methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-({6-[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([4-({[3-(cyclopropylamino) propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-([1-(methoxyacetyl)piperidin-4-yl] methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-([1-(N,N-dimethylglycyl)piperidin-4-yl] methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl] methyl]piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)benzamide;

N-([5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-([trans-4-(morpholin-4-yl)cyclohexyl] methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-N-([4-({[3-(cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(2,2,2-trifluoroethyl)amino)propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino)propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

methyl 2-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenylamino]methyl]morpholine-4-carboxylate;

2-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenylamino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(methylsulfonyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclobutyl(cyclopropyl)amino)propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-({4-cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-[[2-chloro-4-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

(2S)-2-[[3-chloro-5-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl]oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

N-[(5-chloro-6-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-[[3-chloro-5-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-me-



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thylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-([[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-([[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(2,2-difluorocyclopropyl)amino]cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(tet-

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rahydro-2H-pyran-4-ylmethyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(4-cyano-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

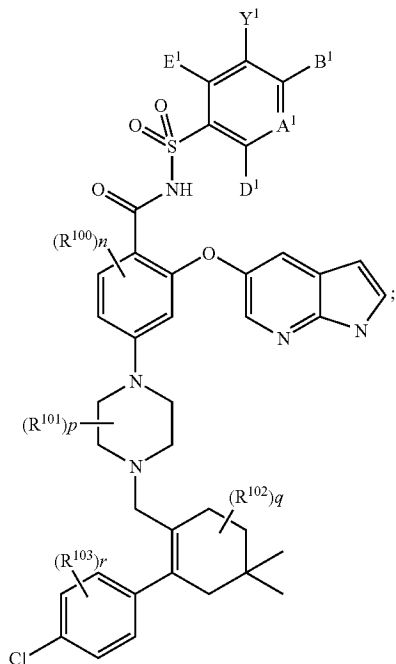
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-([[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino)-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfonyl]-2-nitrophenyl)morpholine-4-carboxamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(methoxymethyl)cyclohexyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.  
 In another aspect, the present invention provides compounds of Formula (III)



and therapeutically acceptable salts, and metabolites thereof, wherein A¹, B¹, D¹, E¹, and Y¹ are as described herein for Formula (I); R¹⁰⁰ is as described for substituents on R²⁶; n is 0, 1, 2, or 3; R¹⁰¹ is as described for substituents on R³⁰; p is 0, 1, 2, 3, 4, 5, or 6; R¹⁰² is as described for substituents on

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R⁴⁰; q is 0, 1, 2, 3, 4, 5, or 6; R¹⁰³ is as described for substituents on R⁵⁸; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (III), n, p, r, and q are each 0.

In one embodiment of Formula (III), A¹ is N. In another embodiment of Formula (III), A¹ is C(A²). In another embodiment of Formula (III), A¹ is C(A²); and A² is H, F, Cl, Br, or I. In another embodiment of Formula (III), A¹ is C(A²); and A² is H.

In one embodiment of Formula (III), B¹ is R¹, OR¹, NHR¹, NHC(O)R¹, F, Cl, Br, or I. In another embodiment of Formula (III), A¹ is C(A²); A² is H; and B¹ is NHR¹. In another embodiment of Formula (III), A¹ is C(A²); A² is H; and B¹ is OR¹. In another embodiment of Formula (III), A¹ is C(A²); A² is H; and B¹ is Cl. In another embodiment of Formula (III), A¹ is N; and B¹ is NHR¹. In another embodiment of Formula (III), A¹ is N; and B¹ is OR¹. In another embodiment of Formula (III), A¹ is N; and B¹ is Cl. In another embodiment of Formula (III), A¹ is N; and B¹ is R¹.

In one embodiment of Formula (III), D¹ is H or Cl. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is NHR¹; and D¹ is H. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is NHR¹; and D¹ is Cl. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is OR¹; and D¹ is H. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is Cl; and D¹ is H. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is R¹; and D¹ is H. In another embodiment of Formula (III), A¹ is N; B¹ is NHR¹; and D¹ is H. In another embodiment of Formula (III), A¹ is N; B¹ is NHR¹; and D¹ is Cl. In another embodiment of Formula (III), A¹ is N; B¹ is OR¹; and D¹ is H. In another embodiment of Formula (III), A¹ is N; B¹ is Cl; and D¹ is H. In another embodiment of Formula (III), A¹ is N; B¹ is R¹; and D¹ is H.

In one embodiment of Formula (III), E¹ is H. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; and E¹ is H. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is NHR¹; E¹ is H; and D¹ is Cl. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is OR¹, D¹ is H; and E¹ is H. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is Cl; D¹ is H; and E¹ is H. In another embodiment of Formula (III), A¹ is N; B¹ is NHR¹; D¹ is H; and E¹ is H. In another embodiment of Formula (III), A¹ is N; B¹ is NHR¹; E¹ is H; and D¹ is Cl. In another embodiment of Formula (III), A¹ is N; B¹ is OR¹; D¹ is H; and E¹ is H. In another embodiment of Formula (III), A¹ is N; B¹ is Cl; D¹ is H; and E¹ is H. In another embodiment of Formula (III), A¹ is N; B¹ is R¹; D¹ is H; and E¹ is H.

In one embodiment of Formula (III), Y¹ is H, CN, NO₂, F, Cl, Br, I, CF₃, R¹⁷, OR¹⁷, SR¹⁷, SO₂R¹⁷, or C(O)NH₂. In another embodiment of Formula (III), Y¹ is H. In another embodiment of Formula (III), Y¹ is CN. In another embodiment of Formula (III), Y¹ is F, Cl, Br, or I. In another embodiment of Formula (III), Y¹ is CF₃. In another embodiment of Formula (III), Y¹ is SR¹⁷. In another embodiment of Formula (III), Y¹ is OR¹⁷. In another embodiment of Formula (III), Y¹ is NO₂. In another embodiment of Formula (III), Y¹ is SO₂R¹⁷; wherein R¹⁷ is as defined herein. In another embodiment of Formula (III), Y¹ is SO₂R¹⁷; wherein R¹⁷ is alkyl. In another embodiment of Formula (III), Y¹ is R¹⁷; wherein R¹⁷ is alkynyl. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; E¹ is H; and Y¹ is NO₂ or SO₂R¹⁷; wherein R¹⁷ is alkyl or alkynyl. In another embodiment of Formula (III), A¹ is C(A²); A² is H; B¹ is NHR¹; D¹ is H; E¹ is H; and Y¹ is NO₂. In another embodi-

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ment of Formula (III), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>17</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (III), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkenyl. In another embodiment of Formula (III), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (III), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (III), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (III), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (III), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (III), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted

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as defined herein. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>; R<sup>60</sup> is heterocycloalkyl; and R<sup>61</sup> is alkyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.

In one embodiment of Formula (III), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted with R<sup>7</sup>, OR<sup>7</sup>, OH, CN, or F. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is substituted with R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, or N(R<sup>7</sup>)<sub>2</sub>.

In one embodiment of Formula (III), R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup> which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>7</sup> is R<sup>8</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>7</sup> is R<sup>9</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>7</sup> is R<sup>10</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>7</sup> is R<sup>11</sup> which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (III), R<sup>8</sup> is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (III), R<sup>9</sup> is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>9</sup> is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>9</sup> is furanyl; which is unsubstituted.

In one embodiment of Formula (III), R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is tetrahydrofuran, tetrahydropyranyl, morpholinyl, dioxan, oxetan, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is cyclohexyl, cyclopropyl,

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cyclobutyl, or bicyclo[2.2.1]heptanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III),  $R^{10}$  is heterocycloalkyl which is fused with  $R^{10A}$ ; and  $R^{10A}$  is heteroarene. In another embodiment of Formula (III),  $R^{10}$  is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (III),  $R^{11}$  is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III),  $R^{11}$  is alkyl. In another embodiment of Formula (III),  $R^{11}$  is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III),  $R^{11}$  is alkyl; which is substituted as defined herein. In another embodiment of Formula (III),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ,  $OR^{12}$ , or  $CF_3$ . In another embodiment of Formula (III),  $R^{11}$  is alkyl; which is substituted with  $OR^{12}$ ;  $R^{12}$  is  $R^{16}$ ; and  $R^{16}$  is alkyl. In another embodiment of Formula (III),  $R^{11}$  is alkyl; which is substituted with  $CF_3$ . In another embodiment of Formula (III),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ;  $R^{12}$  is  $R^{14}$ ; and  $R^{14}$  is heteroaryl.

In one embodiment of Formula (III),

n, p, r, and q are each 0;

$A^1$  is N or  $C(A^2)$ ;

$A^2$  is H, F, Br, I, or Cl;

$B^1$  is  $R^1$ ,  $OR^1$ ,  $NHR^1$ ,  $NHC(O)R^1$ , F, Br, I or Cl;

$D^1$  is H, F, Br, I, or Cl;

$E^1$  is H; and

$Y^1$  is H, CN,  $NO_2$ , F, Cl, Br, I,  $CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ , or  $C(O)NH_2$ ; or

$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and  $A^2$ ,  $D^1$ , and  $E^1$  are independently selected H;

$R^1$  is  $R^4$  or  $R^5$ ;

$R^4$  is cycloalkyl, or heterocycloalkyl;

$R^5$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^7$ ,  $OR^7$ ,  $NHR^7$ ,  $N(R^7)_2$ , CN, OH, F, Cl, Br or I;

$R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$ , or  $R^{11}$ ;

$R^8$  is phenyl;

$R^9$  is heteroaryl;

$R^{10}$  is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with  $R^{10A}$ ;  $R^{10A}$  is heteroarene;

$R^{11}$  is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{12}$ ,  $OR^{12}$  or  $CF_3$ ;

$R^{12}$  is  $R^{14}$  or  $R^{16}$ ;

$R^{14}$  is heteroaryl;

$R^{16}$  is alkyl;

$R^{17}$  is  $R^{21}$ ;

$R^{21}$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{22}$ , F, Cl, Br or I;

$R^{22}$  is  $R^{25}$ ;

$R^{25}$  is heterocycloalkyl;

wherein the cyclic moieties represented by  $Y^1$  and  $B^1$  together,  $R^4$ ,  $R^8$ ,  $R^{10}$ , and  $R^{25}$ , are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $C(O)N(R^{57})_2$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NHS(O)R^{57}$ , OH, CN, (O), F, Cl, Br or I;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl;

$R^{60}$  is cycloalkyl, or heterocycloalkyl;

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$R^{61}$  is alkyl which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $N(R^{62})_2$ ,  $C(O)OH$ , CN, F, Cl, Br or I;

$R^{62}$  is  $R^{65}$ , or  $R^{66}$ ;

$R^{65}$  is cycloalkyl, or heterocycloalkyl;

$R^{66}$  is alkyl which is unsubstituted or substituted with  $OR^{67}$ ;

$R^{67}$  is alkyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ , and  $R^{60}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ , F, Cl, Br or I;

$R^{68}$  is  $R^{71}$  or  $R^{72}$ ;

$R^{71}$  is heterocycloalkyl; and

$R^{72}$  is alkyl, which is unsubstituted or substituted with one or two F.

Still another embodiment pertains to compounds having Formula (III), which are

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-yl-methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;

N-([5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-[(1-acetyl)piperidin-4-yl]amino]-3-nitrophenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(2-methoxyethoxy)ethyl]sulfonyl]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(2-cyanoethyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-([4-bis(cyclopropylmethyl)amino]cyclohexyl)amino]-3-nitrophenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(1-methylpiperidin-4-yl)methyl]amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 3-([4-({[4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl)morpholine-4-carboxylate;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(morpholin-3-ylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-([1-(methylsulfonyl)piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-([1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-([1-(2,2-difluoroethyl)piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(1-cyclopropyl)piperidin-

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4-yl)amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-{{(1-morpholin-4-ylcyclohexyl)methyl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-{{4-(dicyclopropylamino)cyclohexyl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1S)-1-tetrahydro-2H-pyran-4-yl]piperidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-[(4-{{(4-aminotetrahydro-2H-pyran-4-yl)methyl}amino}-3-nitrophenyl)sulfonyl]-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-{{(1S,3R)-3-morpholin-4-ylcyclopentyl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({4-[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(4-[(1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({[3-nitro-4-({(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl} methyl} amino)phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl) piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl) piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

Cis-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{4-(cyclopropylamino)cyclohexyl} amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([3-nitro-4-{{4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-{{[4-{{4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl} amino} sulfonyl)-2-nitrophenoxymethyl}-4-fluoropiperidine-1-carboxylate;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([3-nitro-4-{{4-(4-tetrahydro-2H-pyran-4-ylpiperazin-1-yl)cyclohexyl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl} methoxy)-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([3-nitro-4-{{(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl} amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([3-nitro-4-{{(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl} methyl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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dro-2H-pyran-4-ylpyrrolidin-3-yl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl} amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{(4-methylmorpholin-2-yl)methyl} amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{(2-methoxyethyl)morpholin-2-yl} methyl} amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-{{(4-acetylmorpholin-2-yl)methyl} amino}-3-nitrophenyl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{[trans-4-(fluoromethyl)-1-oxetan-3-yl]pyrrolidin-3-yl} methoxy}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{[4-(fluorotetrahydro-2H-pyran-4-yl)methyl} amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([3-nitro-4-{{[1-oxetan-3-yl]piperidin-4-yl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{[trans-4-(1-cyclobutyl)piperidin-4-yl] amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl] amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{(3S)-1-cyclopropylpyrrolidin-3-yl} amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([3-nitro-4-{{(1-tetrahydrofuran-3-yl)piperidin-4-yl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{(3R)-1-cyclopropylpyrrolidin-3-yl} amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([3-nitro-4-{{(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl} methyl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{[3-hydroxy-2,2-dimethylpropyl] amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-([4-{{[1-(methylsulfonyl)piperidin-3-yl] methyl} amino}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-[(4-[(1-(1-acetylpiperidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1-(2-fluoro-1-(fluoromethyl)ethyl)azetidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1-(methylsulfonyl)pyrrolidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-[(1-(1-acetylpyrrolidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-[(3R)-1-acetylpyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(3-methoxy-2,2-dimethylpropyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1R,3R)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1R,3S)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1S,3R)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1R,3S)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(3-nitro-4-[(3S)-2-oxopiperidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1-(2-fluoro-1-(fluoromethyl)ethyl)azetidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1-cyclopropylpiperidin-4-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1-(2-fluoroethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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pholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(2,2-difluoroethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(3-nitro-4-[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(4-cyclobutyl)morpholin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(3-nitro-4-[(4-tetrahydrofuran-3-yl)morpholin-3-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1-(2-fluoro-1-(fluoromethyl)ethyl)piperidin-4-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(4-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(3-nitro-4-[(3-(trifluoromethoxy)benzyl)amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(3-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(4-difluoromethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-[(4-[(4-(acetylamino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(3-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-({[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-({[methylsulfonyl]amino}cyclohexyl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-yl]methoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-methyl-5-oxopyrrolidin-3-yl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-[(5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-N-[(5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-2-(2-methoxyethoxy)ethyl]morpholin-2-yl}methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyanomethyl)mor-



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pholin-2-yl)methyl}amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(N,N-dimethylglycyl)morpholin-2-yl)methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 (2-{[4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)amino)methyl}morpholin-4-yl)acetic acid;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([4-(oxetan-3-yl)morpholin-2-yl)methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(cyclopropylmorpholin-2-yl)methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-isopropylpiperidin-4-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([4-([1-tert-butylpiperidin-4-yl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(4-fluoro-1-methylpiperi-

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din-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 tert-butyl 4-([4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)amino)piperazine-1-carboxylate;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-(pentafluoro- $\lambda^6$ -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([4-(oxetan-3-yl)piperazin-1-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([3R)-tetrahydrofuran-3-ylamino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4,4-difluorocyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([4-([1-tert-butylpiperidin-4-yl]amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([1-cyclopropylpiperidin-4-yl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([2S)-4-(cyanomethyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlo-

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rophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl] piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

10 N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

15 N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

25 N-[(5-chloro-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(3-furylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

40 N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

45 N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

50 N-[(5-chloro-6-[(1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

55 N-[(5-chloro-6-[(3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-(tetrahydro-2H-pyran-4-yl)methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

60 N-[(5-chloro-6-[(1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

65 N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-

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dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({5-chloro-6-[(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({[5-chloro-6-(2-methoxyethoxy)pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)benzamide;  
 N-({5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[6-(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[6-(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[4-{[3-(cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimeth-

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ylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[4-{[3-(cyclopropyl(2,2,2-trifluoroethyl)amino]propyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-{[1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[4-{[3-(cyclopropyl(oxetan-3-yl)amino]propyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-chloro-6-[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 methyl 2-({[4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate;  
 2-({[4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl)-N-ethyl-N-methylmorpholine-4-carboxamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[4-{[4-(methylsulfonyl)morpholin-2-yl]methyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[4-{[3-(cyclobutyl(cyclopropyl)amino]propyl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[3-chloro-4-(tetrahydrofuran-3-ylmethoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({[4-{[2-(2R)-4-cyclopropyl-



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morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(2S)-4-cyclopropylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-([4-([[(4-cyclopropylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([[(4-cyclopropylmorpholin-2-yl)methyl]amino]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 2-([[(2-chloro-4-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]phenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;  
 (2S)-2-([[(3-chloro-5-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;  
 N-([5-chloro-6-([[(4-cyclopropylmorpholin-2-yl)methyl]amino]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 2-([[(3-chloro-5-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-chloro-6-([5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 N-([5-chloro-6-([[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 15 N-([5-chloro-6-([[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(2,2-difluorocyclopropyl)amino]cyclohexyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(2,2-difluorocyclopropyl)amino]cyclohexyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 40 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 45 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 50 N-([5-chloro-6-([[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 55 N-([5-chloro-6-([[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 60 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(3-cyano-4-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
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4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-{{(cis-4-ethyl-4-hydroxycyclohexyl)methyl}amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[3-nitro-4-(([(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl)amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{4-({4-((2-cyanoethyl)(cyclopropyl)amino)-1-fluorocyclohexyl}methoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] 20  
methyl]piperazin-1-yl)-N-(5-nitro-6-[(tetrahydro-2H-  
pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl)-2-(1H-  
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] 25  
methyl]piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]  
non-7-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo  
[2,3-b]pyridin-5-yl)oxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[(4-cyano-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl]benzamide; 35

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(6-[[[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-(4-[[4-(4-{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide;

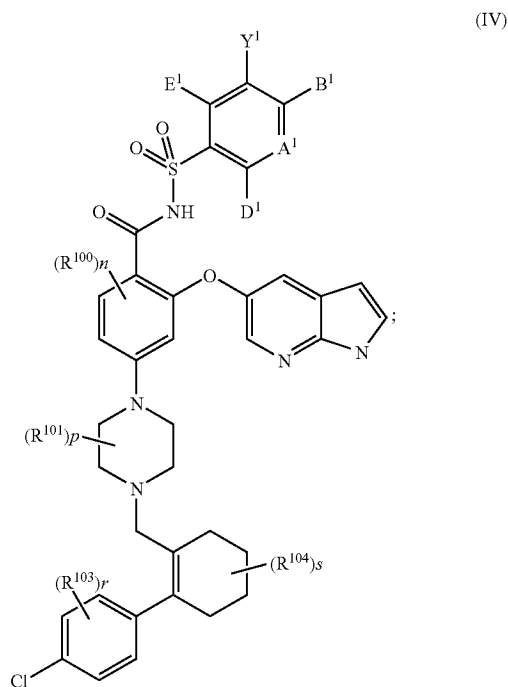
4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-(methoxymethyl)cyclohexyl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(5-chloro-6-[[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[6-[[[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

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In another aspect, the present invention provides compounds of Formula (IV)



and therapeutically acceptable salts, and metabolites thereof, wherein A<sup>1</sup>, B<sup>1</sup>, D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are as described herein for Formula (I); R<sup>100</sup> is as described for substituents on R<sup>26</sup>; n is 0, 1, 2, or 3; R<sup>101</sup> is as described for substituents on R<sup>30</sup>; p is 0, 1, 2, 3, 4, 5, or 6; R<sup>104</sup> is as described for substituents on R<sup>38</sup>; s is 0, 1, 2, 3, 4, 5, or 6; R<sup>103</sup> is as described for substituents on R<sup>58</sup>; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (IV), n, p, r, and s are each 0.

In one embodiment of Formula (IV),  $A^1$  is N. In another embodiment of Formula (IV),  $A^1$  is C( $A^2$ ). In another embodiment of Formula (IV),  $A^1$  is C( $A^2$ ); and  $A^2$  is H, F, Cl, Br, or I. In another embodiment of Formula (IV),  $A^1$  is C( $A^2$ ); and  $A^2$  is H.

In one embodiment of Formula (IV), B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is R<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is N; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is N; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is N; and B<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is N; and B<sup>1</sup> is R<sup>1</sup>.

In one embodiment of Formula (IV), D<sup>1</sup> is H or Cl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N;

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B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H.

In one embodiment of Formula (IV), E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

In one embodiment of Formula (IV), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (IV), Y<sup>1</sup> is H. In another embodiment of Formula (IV), Y<sup>1</sup> is CN. In another embodiment of Formula (IV), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (IV), Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (IV), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (IV), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (IV), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (IV), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (IV), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (IV), Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (IV), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as

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defined herein. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl. In another embodiment of Formula (IV), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.

In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted. In one embodiment of Formula (IV), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted with R<sup>7</sup>, OR<sup>7</sup>, OH, CN, or F. In

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another embodiment of Formula (IV),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is substituted with  $R^7$ ,  $OR^7$ ,  $NHR^7$ , or  $N(R^7)_2$ .

In one embodiment of Formula (IV),  $R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$  or  $R^{11}$  which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^7$  is  $R^8$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^7$  is  $R^9$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^7$  is  $R^{10}$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^7$  is  $R^{11}$  which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (IV),  $R^8$  is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (IV),  $R^9$  is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^9$  is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^9$  is furanyl; which is unsubstituted.

In one embodiment of Formula (IV),  $R^{10}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxan-yl, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is heterocycloalkyl which is fused with  $R^{10A}$ ; and  $R^{10A}$  is heteroarene. In another embodiment of Formula (IV),  $R^{10}$  is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (IV),  $R^{11}$  is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{11}$  is alkyl. In another embodiment of Formula (IV),  $R^{11}$  is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{11}$  is alkyl; which is substituted as defined herein. In another embodiment of Formula (IV),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ,  $OR^{12}$ , or  $CF_3$ . In another embodiment of Formula (IV),  $R^{11}$  is alkyl; which is substituted with  $OR^{12}$ ;  $R^{12}$  is  $R^{16}$ ; and  $R^{16}$  is alkyl. In another embodiment of Formula (IV),  $R^{11}$  is alkyl; which is substituted with  $CF_3$ . In another embodiment of Formula (IV),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ,  $R^{12}$  is  $R^{14}$ , and  $R^{14}$  is heteroaryl.

In one embodiment of Formula (IV),

$n$ ,  $p$ ,  $r$ , and  $s$  are each 0;

$A^1$  is N or C( $A^2$ );

$A^2$  is H, F, Br, I, or Cl;

$B^1$  is  $R^1$ ,  $OR^1$ ,  $NHR^1$ ,  $NHC(O)R^1$ , F, Br, I or Cl;

$D^1$  is H, F, Br, I, or Cl;

$E^1$  is H; and

$Y^1$  is H, CN,  $NO_2$ , F, Cl, Br, I,  $CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ , or  $C(O)NH_2$ ; or

$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and

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$A^2$ ,  $D^1$ , and  $E^1$  are independently selected H;

$R^1$  is  $R^4$  or  $R^5$ ;

$R^4$  is cycloalkyl, or heterocycloalkyl;

$R^5$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^7$ ,  $OR^7$ ,  $NHR^7$ ,  $N(R^7)_2$ , CN, OH, F, Cl, Br or I;

$R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$ , or  $R^{11}$ ;

$R^8$  is phenyl;

$R^9$  is heteroaryl;

$R^{10}$  is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with  $R^{10A}$ ,  $R^{10A}$  is heteroarene;

$R^{11}$  is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{12}$ ,  $OR^{12}$  or  $CF_3$ ;

$R^{12}$  is  $R^{14}$  or  $R^{16}$ ;

$R^{14}$  is heteroaryl;

$R^{16}$  is alkyl;

$R^{17}$  is  $R^{21}$ ;

$R^{21}$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{22}$ , F, Cl, Br or I;

$R^{22}$  is  $R^{25}$ ;

$R^{25}$  is heterocycloalkyl;

wherein the cyclic moieties represented by  $Y^1$  and  $B^1$  together,  $R^4$ ,  $R^8$ ,  $R^{10}$ , and  $R^{25}$ , are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $C(O)N(R^{57})_2$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NHS(O)_2R^{57}$ , OH, CN, (O), F, Cl, Br or I;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl;

$R^{60}$  is cycloalkyl, or heterocycloalkyl;

$R^{61}$  is alkyl which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $N(R^{62})_2$ ,  $C(O)OH$ , CN, F, Cl, Br or I;

$R^{62}$  is  $R^{65}$ , or  $R^{66}$ ;

$R^{65}$  is cycloalkyl, or heterocycloalkyl;

$R^{66}$  is alkyl which is unsubstituted or substituted with  $OR^{67}$ ;

$R^{67}$  is alkyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ , and  $R^{60}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ , F, Cl, Br or I;

$R^{68}$  is  $R^{71}$  or  $R^{72}$ ;

$R^{71}$  is heterocycloalkyl; and

$R^{72}$  is alkyl, which is unsubstituted or substituted with one or two F.

Still another embodiment pertains to compounds having Formula (IV), which are

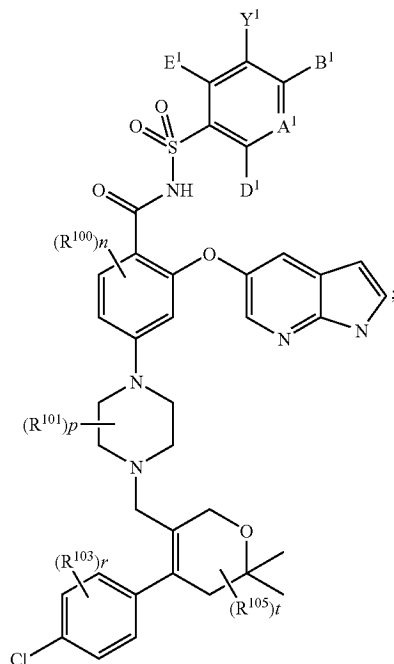
4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (V)

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and therapeutically acceptable salts, and metabolites thereof, wherein A<sup>1</sup>, B<sup>1</sup>, D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are as described herein for Formula (I); R<sup>100</sup> is as described for substituents on R<sup>26</sup>; n is 0, 1, 2, or 3; R<sup>101</sup> is as described for substituents on R<sup>30</sup>; p is 0, 1, 2, 3, 4, 5, or 6; R<sup>105</sup> is as described for substituents on R<sup>40</sup>; t is 0, 1, 2, 3, or 4; R<sup>103</sup> is as described for substituents on R<sup>58</sup>; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (V), n, p, r, and t are each 0.

In one embodiment of Formula (V), A<sup>1</sup> is N. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>). In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); and A<sup>2</sup> is H, F, Cl, Br, or I. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); and A<sup>2</sup> is H.

In one embodiment of Formula (V), B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is R<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is N; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is N; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is N; and B<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is N; and B<sup>1</sup> is R<sup>1</sup>.

In one embodiment of Formula (V), D<sup>1</sup> is H or Cl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H.

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In one embodiment of Formula (V), E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

In one embodiment of Formula (V), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (V), Y<sup>1</sup> is H. In another embodiment of Formula (V), Y<sup>1</sup> is CN. In another embodiment of Formula (V), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (V), Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (V), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (V), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (V), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (V), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (V), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (V), Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (V), Y<sup>1</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (V), Y<sup>1</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl



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ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>; R<sup>60</sup> is heterocycloalkyl; and R<sup>61</sup> is alkyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyran. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.

In one embodiment of Formula (V), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is

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unsubstituted or substituted with R<sup>7</sup>, OR<sup>7</sup>, OH, CN, or F. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is substituted with R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, or N(R<sup>7</sup>)<sub>2</sub>.

In one embodiment of Formula (V), R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup> which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>7</sup> is R<sup>8</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>7</sup> is R<sup>9</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>7</sup> is R<sup>10</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>7</sup> is R<sup>11</sup> which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (V), R<sup>8</sup> is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (V), R<sup>9</sup> is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>9</sup> is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>9</sup> is furanyl; which is unsubstituted.

In one embodiment of Formula (V), R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>10</sup> is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>10</sup> is tetrahydrofuranyl, tetrahydropyran, morpholinyl, dioxanyl, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>10</sup> is tetrahydropyran; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>10</sup> is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>10</sup> is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>10</sup> is heterocycloalkyl which is fused with R<sup>10.4</sup>; and R<sup>10.4</sup> is heteroarene. In another embodiment of Formula (V), R<sup>10</sup> is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (V), R<sup>11</sup> is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>11</sup> is alkyl. In another embodiment of Formula (V), R<sup>11</sup> is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>11</sup> is alkyl; which is substituted as defined herein. In another embodiment of Formula (V), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>, OR<sup>12</sup>, or CF<sub>3</sub>. In another embodiment of Formula (V), R<sup>11</sup> is alkyl; which is substituted with OR<sup>12</sup>; R<sup>12</sup> is R<sup>16</sup>; and R<sup>16</sup> is alkyl. In another embodiment of Formula (V), R<sup>11</sup> is alkyl; which is substituted with CF<sub>3</sub>. In another embodiment of Formula (V), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>; R<sup>12</sup> is R<sup>14</sup>; and R<sup>14</sup> is heteroaryl.

In one embodiment of Formula (V),

n, p, r, and t are each 0;

A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, F, Br, I, or Cl;

B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Br, I or Cl;

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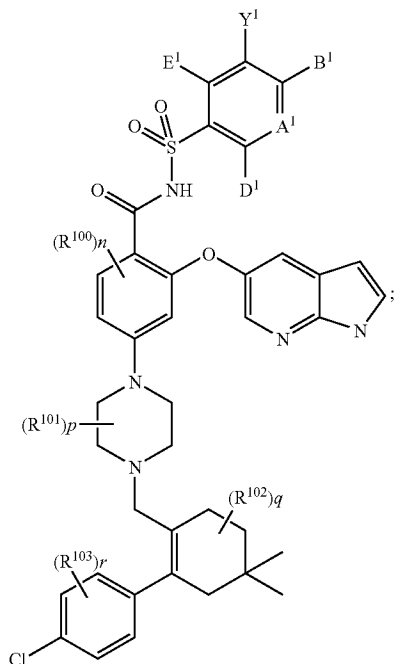
D<sup>1</sup> is H, F, Br, I, or Cl;  
 E<sup>1</sup> is H; and  
 Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>; or  
 Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and  
 A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H;  
 R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>;  
 R<sup>4</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>5</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, CN, OH, F, Cl, Br or I;  
 R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, or R<sup>11</sup>;  
 R<sup>8</sup> is phenyl;  
 R<sup>9</sup> is heteroaryl;  
 R<sup>10</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R<sup>10A</sup>, R<sup>10A</sup> is heteroarene;  
 R<sup>11</sup> is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup> or CF<sub>3</sub>;  
 R<sup>12</sup> is R<sup>14</sup> or R<sup>16</sup>;  
 R<sup>14</sup> is heteroaryl;  
 R<sup>16</sup> is alkyl;  
 R<sup>17</sup> is R<sup>21</sup>;  
 R<sup>21</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, F, Cl, Br or I;  
 R<sup>22</sup> is R<sup>25</sup>;  
 R<sup>25</sup> is heterocycloalkyl;  
 wherein the cyclic moieties represented by Y<sup>1</sup> and B<sup>1</sup> together, R<sup>4</sup>, R<sup>8</sup>, R<sup>10</sup>, and R<sup>25</sup>, are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NHS(O)R<sup>57</sup>, OH, CN, (O), F, Cl, Br or I;  
 R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;  
 R<sup>57</sup> is R<sup>58</sup>, R<sup>60</sup> or R<sup>61</sup>;  
 R<sup>58</sup> is phenyl;  
 R<sup>60</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>61</sup> is alkyl which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, C(O)OH, CN, F, Cl, Br or I;  
 R<sup>62</sup> is R<sup>65</sup>, or R<sup>66</sup>;  
 R<sup>65</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>66</sup> is alkyl which is unsubstituted or substituted with OR<sup>67</sup>;  
 R<sup>67</sup> is alkyl;  
 wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, and R<sup>60</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, F, Cl, Br or I;  
 R<sup>68</sup> is R<sup>71</sup> or R<sup>72</sup>;  
 R<sup>71</sup> is heterocycloalkyl; and  
 R<sup>72</sup> is alkyl, which is unsubstituted or substituted with one or two F.  
 Still another embodiment pertains to a compound having Formula (V), which is

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4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 and therapeutically acceptable salts, and metabolites thereof.  
 In another aspect, the present invention provides compounds of Formula (VI)

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and therapeutically acceptable salts, and metabolites thereof, wherein  $A^1$ ,  $B^1$ ,  $D^1$ ,  $E^1$ , and  $Y^1$  are as described herein for Formula (I);  $R^{100}$  is as described for substituents on  $R^{26}$ ;  $n$  is 0, 1, 2, or 3;  $R^{101}$  is as described for substituents on  $R^{30}$ ;  $p$  is 0, 1, 2, 3, 4, 5, or 6;  $R^{102}$  is as described for substituents on  $R^{40}$ ;  $q$  is 0, 1, 2, 3, 4, 5, or 6;  $R^{103}$  is as described for substituents on  $R^{58}$ ; and  $r$  is 0, 1, 2, 3, or 4.

In one embodiment of Formula (VI),  $n$ ,  $p$ ,  $r$ , and  $q$  are each 0.

In one embodiment of Formula (VI),  $A^1$  is N. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ . In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ; and  $A^2$  is H, F, Cl, Br, or I. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ; and  $A^2$  is H.

In one embodiment of Formula (VI),  $B^1$  is  $R^1$ ,  $OR^1$ ,  $NHR^1$ ,  $NHC(O)R^1$ , F, Cl, Br, or I. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H; and  $B^1$  is  $NHR^1$ . In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H; and  $B^1$  is  $OR^1$ . In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H; and  $B^1$  is Cl. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H; and  $B^1$  is  $R^1$ . In another embodiment of Formula (VI),  $A^1$  is N; and  $B^1$  is  $NHR^1$ . In another embodiment of Formula (VI),  $A^1$  is N; and  $B^1$  is  $OR^1$ . In another embodiment of Formula (VI),  $A^1$  is N; and  $B^1$  is Cl. In another embodiment of Formula (VI),  $A^1$  is N; and  $B^1$  is  $R^1$ .

In one embodiment of Formula (VI),  $D^1$  is H or Cl. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $NHR^1$ ; and  $D^1$  is H. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $NHR^1$ ; and  $D^1$  is Cl. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $OR^1$ ; and  $D^1$  is H. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is Cl; and  $D^1$  is H. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $R^1$ ; and  $D^1$  is H. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $NHR^1$ ; and  $D^1$  is H. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $NHR^1$ ; and  $D^1$  is Cl. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $OR^1$ ; and  $D^1$  is H. In another embodiment

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of Formula (VI),  $A^1$  is N;  $B^1$  is Cl; and  $D^1$  is H. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $R^1$ ; and  $D^1$  is H.

In one embodiment of Formula (VI),  $E^1$  is H. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $NHR^1$ ;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $NHR^1$ ;  $E^1$  is H; and  $D^1$  is Cl. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $OR^1$ ;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is Cl;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $R^1$ ;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $NHR^1$ ;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $NHR^1$ ;  $E^1$  is H; and  $D^1$  is Cl. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $OR^1$ ;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is Cl;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $R^1$ ;  $D^1$  is H; and  $E^1$  is H.

In one embodiment of Formula (VI),  $Y^1$  is H, CN,  $NO_2$ , F, Cl, Br, I,  $CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ , or  $C(O)NH_2$ . In another embodiment of Formula (VI),  $Y^1$  is H. In another embodiment of Formula (VI),  $Y^1$  is CN. In another embodiment of Formula (VI),  $Y^1$  is F, Cl, Br, or I. In another embodiment of Formula (VI),  $Y^1$  is  $CF_3$ . In another embodiment of Formula (VI),  $Y^1$  is  $SR^{17}$ . In another embodiment of Formula (VI),  $Y^1$  is  $OR^{17}$ . In another embodiment of Formula (VI),  $Y^1$  is  $NO_2$ . In another embodiment of Formula (VI),  $Y^1$  is  $SO_2R^{17}$ ; wherein  $R^{17}$  is as defined herein. In another embodiment of Formula (VI),  $Y^1$  is  $SO_2R^{17}$ ; wherein  $R^{17}$  is alkyl. In another embodiment of Formula (VI),  $Y^1$  is  $R^{17}$ ; wherein  $R^{17}$  is alkynyl. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $NHR^1$ ;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is  $NO_2$  or  $SO_2R^{17}$ ; wherein  $R^{17}$  is alkyl or alkynyl. In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $NHR^1$ ;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is  $NO_2$ . In another embodiment of Formula (VI),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $NHR^1$ ;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is  $SO_2R^{17}$ ; wherein  $R^{17}$  is alkyl substituted with three F. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $NHR^1$ ;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is  $NO_2$  or  $SO_2R^{17}$ ; wherein  $R^{17}$  is alkyl or alkynyl. In another embodiment of Formula (VI),  $A^1$  is N;  $B^1$  is  $NHR^1$ ;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is  $NO_2$ . In another embodiment of Formula (VI),  $A^1$  is N;  $D^1$  is  $NHR^1$ ;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is  $SO_2R^{17}$ ; wherein  $R^{17}$  is alkyl substituted with three F.

In one embodiment of Formula (IV),  $Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV),  $Y^1$  and  $D^1$ , together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (IV),  $A^1$  is  $C(A^2)$ ;  $A^2$ ,  $G^1$ ,  $E^1$ , and  $D^1$  are independently selected H; and  $Y^1$  and  $D^1$ , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV),  $A^1$  is  $C(A^2)$ ;  $A^2$ ,  $G^1$ ,  $E^1$ , and  $D^1$  are independently selected H; and  $Y^1$  and  $D^1$ , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (VI),  $R^1$  is  $R^4$  or  $R^5$ . In one embodiment of Formula (VI),  $R^1$  is  $R^4$ . In one embodiment of Formula (VI),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (VI),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (VI),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl. In one embodiment of Formula (VI),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl.

In one embodiment of Formula (VI),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein  $R^4$  is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is sub-

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stituted as defined herein. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl R<sup>60</sup> is heterocycloalkyl; and R<sup>61</sup> is alkyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranlyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.

In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted. In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted with R<sup>7</sup>, OR<sup>7</sup>, OH, CN, or F. In

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another embodiment of Formula (VI), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is substituted with R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, or N(R<sup>7</sup>)<sub>2</sub>.

In one embodiment of Formula (VI), R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup> which are unsubstituted or substituted as defined herein.

In another embodiment of Formula (VI), R<sup>7</sup> is R<sup>8</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>7</sup> is R<sup>9</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>7</sup> is R<sup>10</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>7</sup> is R<sup>11</sup> which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (VI), R<sup>8</sup> is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (VI), R<sup>9</sup> is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>9</sup> is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>9</sup> is furanyl; which is unsubstituted.

In one embodiment of Formula (VI), R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is tetrahydrofuranyl, tetrahydropyranlyl, morpholinyl, dioxanlyl, oxetanyl, piperidinyl, or pyrrolidinyl; which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is tetrahydropyranlyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is heterocycloalkyl which is fused with R<sup>10,4</sup>, and R<sup>10,4</sup> is heteroarene. In another embodiment of Formula (VI), R<sup>10</sup> is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (VI), R<sup>11</sup> is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl. In another embodiment of Formula (VI), R<sup>11</sup> is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl; which is substituted as defined herein. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>, OR<sup>12</sup>, or CF<sub>3</sub>. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl, which is substituted with OR<sup>12</sup>; R<sup>12</sup> is R<sup>16</sup>; and R<sup>16</sup> is alkyl. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl; which is substituted with CF<sub>3</sub>. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl, which is substituted with R<sup>12</sup>; R<sup>12</sup> is R<sup>14</sup>; and R<sup>14</sup> is heteroaryl.

In one embodiment of Formula (VI),

n, p, r, and q are each 0;

A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, F, Br, I, or Cl;

B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Br, I or Cl;

D<sup>1</sup> is H, F, Br, I, or Cl;

E<sup>1</sup> is H; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>; or

Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and



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A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H;  
 R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>;  
 R<sup>4</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>5</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, CN, OH, F, Cl, Br or I;  
 R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, or R<sup>11</sup>;  
 R<sup>8</sup> is phenyl;  
 R<sup>9</sup> is heteroaryl;  
 R<sup>10</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R<sup>10A</sup>, R<sup>10A</sup> is heteroarene;  
 R<sup>11</sup> is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup> or CF<sub>3</sub>;  
 R<sup>12</sup> is R<sup>14</sup> or R<sup>16</sup>;  
 R<sup>14</sup> is heteroaryl;  
 R<sup>16</sup> is alkyl;  
 R<sup>17</sup> is R<sup>21</sup>;  
 R<sup>21</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, F, Cl, Br or I;  
 R<sup>22</sup> is R<sup>25</sup>;  
 R<sup>25</sup> is heterocycloalkyl;  
 wherein the cyclic moieties represented by Y<sup>1</sup> and B<sup>1</sup> together, R<sup>4</sup>, R<sup>8</sup>, R<sup>10</sup>, and R<sup>25</sup>, are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NHS(O)R<sup>57</sup>, OH, CN, (O), F, Cl, Br or I;  
 R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;  
 R<sup>57</sup> is R<sup>58</sup>, R<sup>11</sup> or R<sup>61</sup>;  
 R<sup>58</sup> is phenyl;  
 R<sup>60</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>61</sup> is alkyl which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, C(O)OH, CN, F, Cl, Br or I;  
 R<sup>62</sup> is R<sup>65</sup>, or R<sup>66</sup>;  
 R<sup>65</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>66</sup> is alkyl which is unsubstituted or substituted with OR<sup>67</sup>;  
 R<sup>67</sup> is alkyl;  
 wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, and R<sup>60</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, F, Cl, Br or I;  
 R<sup>68</sup> is R<sup>71</sup> or R<sup>72</sup>;  
 R<sup>71</sup> is heterocycloalkyl; and  
 R<sup>72</sup> is alkyl, which is unsubstituted or substituted with one or two F.

Still another embodiment pertains to a compound having Formula (VI), which is

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts, and metabolites thereof.

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Pharmaceutical Compositions, Combination Therapies, Methods of Treatment, and Administration

Another embodiment comprises pharmaceutical compositions comprising a compound having Formula (I) and an excipient.

Still another embodiment comprises methods of treating cancer in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having Formula (I).

Still another embodiment comprises methods of treating autoimmune disease in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating diseases during which anti-apoptotic Bcl-2 proteins are expressed, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I).

Still another embodiment pertains to methods of treating disease in a patient during which anti-apoptotic Bcl-2 proteins are expressed, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I).

Still another embodiment pertains to methods of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating diseases during which are expressed anti-apoptotic Bcl-2 proteins, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating disease in a patient during which are expressed anti-apoptotic Bcl-2 proteins, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to compositions for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia,

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mia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Metabolites of compounds having Formula (I), produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases associated with anti-apoptotic Bcl-2 proteins.

Certain precursor compounds which may be metabolized in vitro or in vivo to form compounds having Formula (I) may also have utility for treating diseases associated with expression of anti-apoptotic Bcl-2 proteins.

Compounds having Formula (I) may exist as acid addition salts, basic addition salts or zwitterions. Salts of the compounds are prepared during isolation or following purification of the compounds. Acid addition salts of the compounds are those derived from the reaction of the compounds with an acid. For example, the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylsulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, para-toluenesulfonate, and undecanoate salts of the compounds are contemplated as being embraced by this invention. Basic addition salts of the compounds are those derived from the reaction of the compounds with the hydroxide, carbonate or bicarbonate of cations such as lithium, sodium, potassium, calcium, and magnesium.

The compounds having Formula (I) may be administered, for example, buccally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperitoneally, intrasternally, intravenously, subcutaneously), rectally, topically, transdermally or vaginally.

Therapeutically effective amounts of compounds having Formula (I) depend on the recipient of the treatment, the disorder being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered. The amount of a compound of this invention having Formula (I) used to make a composition to be administered daily to a patient in a single dose or in divided doses is from about 0.03 to about 200 mg/kg body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

Compounds having Formula (I) may be administered with or without an excipient. Excipients include, for example,

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encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

Excipients for preparation of compositions comprising a compound having Formula (I) to be administered orally in solid dosage form include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered ophthalmically or orally in liquid dosage forms include, for example, 1,3-butylene glycol, castor oil, corn oil, cottonseed oil, ethanol, fatty acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered osmotically include, for example, chlorofluorohydrocarbons, ethanol, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered parenterally include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered rectally or vaginally include, for example, cocoa butter, polyethylene glycol, wax and mixtures thereof.

Compounds having Formula (I) are expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, other apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNA's, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum che-

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motherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, etinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, and the like, and in combination with one or more of these agents.

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (V. R. Sutton, D. L. Vaux and J. A. Trapani, *J. of Immunology* 1997, 158 (12), 5783).

siRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxy-nucleotide, 2'-OCH<sub>3</sub>-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/or the 3'-ends of a given strand. For example, siRNAs targeting Mcl-1 have been shown to enhance the activity of ABT-263, (i.e., N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide) or ABT-737 (i.e., N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) in multiple tumor cell lines (Tse et al, *Cancer Research* 2008, 68(9), 3421 and references therein).

Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

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Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, CLORE-TAZINE® (laromustine, VNP 40101M), cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepe, TRE-ANDA® (bendamustine), treosulfan, rofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

Antimetabolites include ALIMTA® (pemetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA® (capecitabine), carmofofur, LEUSTAT® (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-(3-D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethnylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR® (gemcitabine), hydroxyurea, ALKERAN® (melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

Antivirals include ritonavir, hydroxychloroquine and the like.

Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, Aurora A-specific kinase inhibitors, Aurora B-specific kinase inhibitors and pan-Aurora kinase inhibitors and the like.

Bcl-2 protein inhibitors include AT-101 ((-)gossypol), GENASENSE® (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4'-(4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(4IR)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide (ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263), GX-070 (obatoclox) and the like.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (imatinib) and the like.

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

COX-2 inhibitors include ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX® (celecoxib), COX-189 (lumiracoxib), CT-3, DERA-MAXX® (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole), MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) and the like.

EGFR inhibitors include ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX® (cetuximab), HR<sup>3</sup>, IgA antibodies, IRESSA® (gefitinib),



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TARCEVA® (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB® (lapatinib) and the like.

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), HERCEPTIN® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (2C4, pertuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 tri-functional bispecific antibodies, mAB AR-209, mAB 2B-1 and the like.

Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB® (human recombinant antibody to HSP-90), NCS-683664, PU24FCI, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

Inhibitors of inhibitors of apoptosis proteins include HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

Antibody drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am, SGN-35, SGN-75 and the like.

Activators of death receptor pathway include TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR<sup>4</sup> and DR<sup>5</sup>) such as Apomab, conatumumab, ETR2-ST01, GDC0145, (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

Kinesin inhibitors include Eg5 inhibitors such as AZD4877, ARRY-520; CENPE inhibitors such as GSK923295A and the like.

JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCB018424 and the like.

MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, Torin 1 and the like.

Non-steroidal anti-inflammatory drugs include AMIGESIC® (salsalate), DOLOBID® (diflunisal), MOTRIN® (ibuprofen), ORUDIS® (ketoprofen), RELAFEN® (nabumetone), FELDENE® (piroxicam), ibuprofen cream, ALEVE® (naproxen) and NAPROSYN® (naproxen), VOLTAREN® (diclofenac), INDOCIN® (indomethacin), CLINORIL® (sulindac), TOLECTIN® (tolmetin), LODINE® (etodolac), TORADOL® (ketorolac), DAYPRO® (oxaprozin) and the like.

PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

Platinum chemotherapeutics include cisplatin, ELOXATIN® (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN® (carboplatin), satraplatin, picoplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

Phosphoinositide-3 kinase (PI3K) inhibitors include wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

VEGFR inhibitors include AVASTIN (bevacizumab), ABT-869, AEE-788, ANGIOZYME™ (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, Colo.) and Chiron, (Emeryville, Calif.)), axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pe-

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gaptamib), NEXAVAR® (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), VEGF trap, ZACTIMA™ (vandetanib, ZD-6474) and the like.

Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE® (bleomycin), daunorubicin, CAELYX® or MYOCET® (liposomal doxorubicin), elsamitrucin, epirubicin, glarbuicin, ZAVEDOS® (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR® (valrubicin), zinostatin and the like.

Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR® (irinotecan hydrochloride), camptothecin, CARD10xANE® (dexrazoxine), diflomotecan, edotecarin, ELLENCE® or PHARMORUBICIN® (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, taf-luposide, topotecan and the like.

Antibodies include AVASTIN® (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzimab, CD20 antibodies types I and II and the like.

Hormonal therapies include ARIMIDEX® (anastrozole), AROMASIN® (exemestane), arzoxifene, CASODEX® (bicalutamide), CETROTIDE® (cetorelix), degarelix, deslorelin, DESOPAN® (trilostane), dexamethasone, DROGENIL® (flutamide), EVISTA® (raloxifene), AFEMA™ (fadrozole), FARESTON® (toremifene), FASLODEX® (fulvestrant), FEMARA® (letrozole), formestane, glucocorticoids, HECTOROL® (doxercalciferol), RENAGEL® (sevelamer carbonate), lasofoxifene, leuprolide acetate, MEGACE® (megesterol), MIFEPREX® (mifepristone), NILANDRON™ (nilutamide), NOLVADEX® (tamoxifen citrate), PLENAXIS™ (abarelix), prednisone, PROPECIA® (finasteride), rilostane, SUPREFACT® (buserelin), TRELSTAR® (luteinizing hormone releasing hormone (LHRH)), VANTAS® (Histrelin implant), VETORYL® (trilostane or modrastane), ZOLADEX® (fosreltin, goserelin) and the like.

Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN® (alitretinoin), ATRAGEN® (liposomal tretinoin), TARGRETIN® (bexarotene), LGD-1550 and the like.

PARP inhibitors include ABT-888 (veliparib), olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

Proteasome inhibitors include VELCADE (bortezomib), MG132, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE® (interferon gamma-1b) or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE®, (IFN-α), BAM-002 (oxidized glutathione), BEROMUN® (tasonermin), BEXXAR® (tositumomab), CAMPATH® (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE® (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab,



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molgramostim, MYLOTARG™ (gemtuzumab ozogamicin), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pentumomab (Y-muHMF1), PROVENGE® (sipuleucel-T), sargamostim, sizofilan, teceleukin, THERACYS® (Bacillus Calmette-Guerin), ubenimex, VIRULIZIN® (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodecaoxide (TCDO)), PROLEUKIN® (aldesleukin), ZADAXIN® (thymalfasin), ZENAPAX® (dacizumab), ZEVALIN® (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofuran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA® (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR® (gemcitabine), TOMUDEX® (ratitrexed), TROXATYL™ (triacetylruridine troxatibine) and the like.

Purine analogs include LANVIS® (thioguanine) and PURI-NETHOL® (mercaptapurine).

Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilone, XRP-9881 (larotaxel), vinflunine, ZK-EPO (synthetic epothilone) and the like.

Ubiquitin ligase inhibitors include MDM2 inhibitors, such as nutlins, NEDD8 inhibitors such as MLN4924 and the like.

Compounds of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy and the like.

Additionally, compounds having Formula (I) may be combined with other chemotherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN® (Ad5CMV-p53 vaccine), ALTOCOR® or MEVACOR® (lovastatin), AMPLIGEN® (poly I:poly C12U, a synthetic RNA), APTOSYN® (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), AVAGE® (tazarotene), AVE-8062 (combreastatin derivative) BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CEAVAC® (cancer vaccine), CELEUK® (celmoleukin), CEPLINE® (histamine dihydrochloride), CERVARIX® (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CYPAT™ (cyproterone acetate), combrestatin A4P, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor) or TransMID-107R™ (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthene-4-acetic acid (DMXAA), eniluracil, EVI-ZON™ (squalamine lactate), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EP0906 (epithilone B), GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), GASTRIMMUNE®, GENA-SENSE®, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas

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exotoxin, interferon- $\alpha$ , interferon- $\gamma$ , JUNOVAN™ or MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTATAAE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), ONCOVAX® (IL-2 Vaccine), ORATHECIN™ (rubitecan), OSIDEM® (antibody-based cell drug), OVAREX® MAb (murine monoclonal antibody), paclitaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REV-LIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN® (bexarotene), TAXOPREXIN® (DHA-paclitaxel), TELCYTA® (canfosfamide, TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFERADE™ (adenovector: DNA carrier containing the gene for tumor necrosis factor- $\alpha$ ), TRACLEER® or ZAVESCA® (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX® (arsenic trioxide), VIRULIZIN®, ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti-alphavbeta3 antibody), XCYTRIN® (motexafin gadolinium), XINLAY™ (atrasentan), XYO-TAX™ (paclitaxel poliglumex), YONDELIS® (trabectedin), ZD-6126, ZINECARD® (dexrazoxane), ZOMETA® (zoledronic acid), zorubicin and the like.

Data

Determination of the utility of compounds having Formula (I) as binders to and inhibitors of anti-apoptotic Bcl-2 proteins was performed using the Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) Assay. Tb-anti-GST antibody was purchased from Invitrogen (Catalog No. PV4216).

#### Probe Synthesis

All reagents were used as obtained from the vendor unless otherwise specified. Peptide synthesis reagents including diisopropylethylamine (DIEA), dichloromethane (DCM), N-methylpyrrolidone (NMP), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), N-hydroxybenzotriazole (HOBt) and piperidine were obtained from Applied Biosystems, Inc. (ABI), Foster City, Calif. or American Bioanalytical, Natick, Mass. Preloaded 9-Fluorenylmethyloxycarbonyl (Fmoc) amino acid cartridges (Fmoc-Ala-OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Phe-OH, Fmoc-Gly-OH, Fmoc-His(Trt)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Pro-OH, Fmoc-Gln(Trt)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Val-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(tBu)-OH) were obtained from ABI or Anaspec, San Jose, Calif. The peptide synthesis resin (Fmoc-Rink amide MBHA resin) and Fmoc-Lys(Mtt)-OH were obtained from Novabiochem, San Diego, Calif. Single-isomer 6-carboxyfluorescein succinimidyl ester (6-FAM-NHS) was obtained from Anaspec. Trifluoroacetic acid (TFA) was obtained from Oakwood Products, West Columbia, S.C. Thioanisole, phenol, triisopropylsilane (TIS), 3,6-dioxo-1,8-octanedithiol (DODT) and isopropanol were obtained from Aldrich Chemical Co., Milwaukee, Wis.

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Matrix-assisted laser desorption ionization mass-spectra (MALDI-MS) were recorded on an Applied Biosystems Voyager DE-PRO MS). Electrospray mass-spectra (ESI-MS) were recorded on Finnigan SSQ7000 (Finnigan Corp., San Jose, Calif.) in both positive and negative ion mode.

#### General Procedure for Solid-Phase Peptide Synthesis (SPPS)

Peptides were synthesized with, at most, 250  $\mu$ mol pre-loaded Wang resin/vessel on an ABI 433A peptide synthesizer using 250  $\mu$ mol scale FASTMOC™ coupling cycles. Preloaded cartridges containing 1 mmol standard Fmoc-amino acids, except for the position of attachment of the fluorophore, where 1 mmol Fmoc-Lys(Mtt)-OH was placed in the cartridge, were used with conductivity feedback monitoring. N-terminal acetylation was accomplished by using 1 mmol acetic acid in a cartridge under standard coupling conditions.

#### Removal of 4-Methyltrityl (Mtt) from Lysine

The resin from the synthesizer was washed thrice with DCM and kept wet. 150 mL of 95:4:1 dichloromethane:triisopropylsilane:trifluoroacetic acid was flowed through the resin bed over 30 minutes. The mixture turned deep yellow then faded to pale yellow. 100 mL of DMF was flowed through the bed over 15 minutes. The resin was then washed thrice with DMF and filtered. Ninhydrin tests showed a strong signal for primary amine.

#### Resin Labeling with 6-Carboxyfluorescein-NHS (6-FAM-NHS)

The resin was treated with 2 equivalents 6-FAM-NHS in 1% DIEA/DMF and stirred or shaken at ambient temperature overnight. When complete, the resin was drained, washed thrice with DMF, thrice with (1 $\times$  DCM and 1 $\times$  methanol) and dried to provide an orange resin that was negative by ninhydrin test.

#### General Procedure for Cleavage and Deprotection of Resin-Bound Peptide

Peptides were cleaved from the resin by shaking for 3 hours at ambient temperature in a cleavage cocktail consisting of 80% TFA, 5% water, 5% thioanisole, 5% phenol, 2.5% TIS, and 2.5% EDT (1 mL/0.1 g resin). The resin was removed by filtration and rinsing twice with TFA. The TFA was evaporated from the filtrates, and product was precipitated with ether (10 mL/0.1 g resin), recovered by centrifugation, washed twice with ether (10 mL/0.1 g resin) and dried to give the crude peptide.

#### General Procedure for Purification of Peptides

The crude peptides were purified on a Gilson preparative HPLC system running Unipoint® analysis software (Gilson, Inc., Middleton, Wis.) on a radial compression column containing two 25 $\times$ 100 mm segments packed with Delta-Pak™ C18 15  $\mu$ m particles with 100 Å pore size and eluted with one of the gradient methods listed below. One to two milliliters of crude peptide solution (10 mg/mL in 90% DMSO/water) was purified per injection. The peaks containing the product(s) from each run were pooled and lyophilized. All preparative

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runs were run at 20 mL/min with eluents as buffer A: 0.1% TFA-water and buffer B: acetonitrile.

#### General Procedure for Analytical HPLC

Analytical HPLC was performed on a Hewlett-Packard 1200 series system with a diode-array detector and a Hewlett-Packard 1046A fluorescence detector running HPLC 3D CHEMSTATION software version A.03.04 (Hewlett-Packard, Palo Alto, Calif.) on a 4.6 $\times$ 250 mm YMC column packed with ODS-AQ 5  $\mu$ m particles with a 120 Å pore size and eluted with one of the gradient methods listed below after preequilibrating at the starting conditions for 7 minutes. Eluents were buffer A: 0.1% TFA-water and buffer B: acetonitrile. The flow rate for all gradients was 1 mL/min.

(SEQ ID NO: 1)

F-Bak: Peptide Probe Acetyl-GQVGRQLAIIIGDK  
(6-FAM) INR-NH<sub>2</sub>

Fmoc-Rink amide MBHA resin was extended using the general peptide synthesis procedure to provide the protected resin-bound peptide (1.020 g). The Mtt group was removed, labeled with 6-FAM-NHS and cleaved and deprotected as described hereinabove to provide the crude product as an orange solid (0.37 g). This product was purified by RP-HPLC. Fractions across the main peak were tested by analytical RP-HPLC, and the pure fractions were isolated and lyophilized, with the major peak providing the title compound (0.0802 g) as a yellow solid; MALDI-MS  $m/z$ =2137.1 [(M+H)<sup>+</sup>].

(SEQ ID NO: 1)

Alternative Synthesis of Peptide Probe F-Bak:  
Acetyl-GQVGRQLAIIIGDK (6-FAM) INR-NH<sub>2</sub>

The protected peptide was assembled on 0.25 mmol Fmoc-Rink amide MBHA resin (Novabiochem) on an Applied Biosystems 433A automated peptide synthesizer running FAST-MOC™ coupling cycles using pre-loaded 1 mmol amino acid cartridges, except for the fluorescein(6-FAM)-labeled lysine, where 1 mmol Fmoc-Lys(4-methyltrityl) was weighed into the cartridge. The N-terminal acetyl group was incorporated by putting 1 mmol acetic acid in a cartridge and coupling as described hereinabove. Selective removal of the 4-methyltrityl group was accomplished with a solution of 95:4:1 DCM: TIS:TFA (v/v/v) flowed through the resin over 15 minutes, followed by quenching with a flow of dimethylformamide. Single-isomer 6 carboxyfluorescein-NHS was reacted with the lysine side-chain in 1% DIEA in DMF and confirmed complete by ninhydrin testing. The peptide was cleaved from the resin and side-chains deprotected by treating with 80:5: 5:5:2.5:2.5 TFA/water/phenol/thioanisole/triisopropylsilane: 3,6-dioxo-1,8-octanedithiol (v/v/v/v/v/v), and the crude peptide was recovered by precipitation with diethyl ether. The crude peptide was purified by reverse-phase high-performance liquid chromatography, and its purity and identity were confirmed by analytical reverse-phase high-performance liquid chromatography and matrix-assisted laser-desorption mass-spectrometry ( $m/z$ =2137.1 ((M+H)<sup>+</sup>)).

#### Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) Assay

Representative compounds were serially diluted in dimethyl sulfoxide (DMSO) starting at 50  $\mu$ M (2 $\times$  starting concentration; 10% DMSO) and 10  $\mu$ L were transferred into a

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384-well plate. Then 10  $\mu$ L of a protein/probe/antibody mix was added to each well at final concentrations listed in TABLE 1. The samples are then mixed on a shaker for 1 minute and incubated for an additional 3 hours at room temperature. For each assay, the probe/antibody and protein/probe/antibody were included on each assay plate as negative and positive controls, respectively. Fluorescence was measured on the ENVISION plate reader (Perkin Elmer) using a 340/35 nm excitation filter and 520/525 (F-Bak peptide) and 495/510 nm (Tb-labeled anti-Histidine antibody) emission filters. Dissociation constants ( $K_i$ ) are shown in TABLE 2 below and were determined using Wang's equation (Wang Z.-X. An Exact Mathematical Expression For Describing Competitive Binding Of Two Different Ligands To A Protein Molecule. *FEBS Lett.* 1995, 360:111-4).

TABLE 1

| Protein, Probe And Antibody Used For TR-FRET Assays    |       |              |             |          |               |
|--|-------|--------------|-------------|----------|---------------|
| Protein  | Probe | Protein (nM) | Probe (nM)  | Antibody | Antibody (nM) |
| GST-Bcl-2 F-Bak Peptide Probe                          | 1     | 100          | Tb-anti-GST | 1        |               |
| Acetyl-GQVGRQLAIIIGDK (6-FAM) INR-amide (SEQ ID NO: 1) |       |              |             |          |               |

6-FAM = 6-carboxyfluorescein.; Tb = terbium; GST = glutathione S-transferase

The samples were then mixed on a shaker for 1 minute and incubated for an additional 3 hours at room temperature. For each assay, the probe/antibody and protein/probe/antibody were included on each assay plate as negative and positive controls, respectively. Fluorescence was measured on the Envision (Perkin Elmer) using a 340/35 nm excitation filter and 520/525 (F-Bak peptide) and 495/510 nm (Tb-labeled anti-Histidine antibody) emission filters.

Inhibition constants ( $K_i$ ) for compounds according to the invention are shown in TABLE 2 below. Where the  $K_i$  for a compound is represented as "<" (less than) a certain numerical value, it is intended to mean that the binding affinity value (e.g., for Bcl-2) is lower than the limit of detection of the assay used. Inhibition constants were determined using Wang's equation (Wang Zx, An Exact Mathematical Expression For Describing Competitive Binding Of Two Different Ligands To A Protein Molecule. *FEBS Lett.* 1995, 360:111-4).

TABLE 2

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 1                                      | 0.000225  |
| 2                                      | <0.000010 |
| 3                                      | 0.000013  |
| 4                                      | <0.000010 |
| 5                                      | <0.000010 |
| 6                                      | 0.000018  |
| 7                                      | 0.00492   |
| 8                                      | 0.000153  |
| 9                                      | <0.000010 |
| 10                                     | <0.000010 |
| 11                                     | 0.000016  |
| 12                                     | <0.000010 |
| 13                                     | <0.000010 |
| 14                                     | 0.002798  |
| 15                                     | <0.000010 |
| 16                                     | 0.000219  |
| 17                                     | 0.00009   |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 18                                     | 0.000017  |
| 19                                     | 0.000226  |
| 20                                     | 0.000181  |
| 21                                     | 0.000912  |
| 22                                     | 0.000291  |
| 23                                     | 0.000083  |
| 24                                     | <0.000010 |
| 25                                     | <0.000010 |
| 26                                     | 0.000011  |
| 27                                     | 0.000134  |
| 28                                     | <0.000010 |

TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 29                                     | <0.000010 |
| 30                                     | <0.000010 |
| 31                                     | <0.000010 |
| 32                                     | <0.000010 |
| 33                                     | <0.000010 |
| 34                                     | 0.00001   |
| 35                                     | <0.000010 |
| 36                                     | 0.000017  |
| 37                                     | <0.000010 |
| 38                                     | 0.0003    |
| 39                                     | 0.000012  |
| 40                                     | <0.000010 |
| 41                                     | <0.000010 |
| 42                                     | 0.000439  |
| 43                                     | 0.000012  |
| 44                                     | <0.000010 |
| 45                                     | <0.000010 |
| 46                                     | 0.000935  |
| 47                                     | <0.000010 |
| 48                                     | <0.000010 |
| 49                                     | 0.000074  |
| 50                                     | 0.000021  |
| 51                                     | <0.000010 |
| 52                                     | 0.000114  |
| 53                                     | <0.000010 |
| 54                                     | 0.002071  |
| 55                                     | <0.000010 |
| 56                                     | 0.000037  |
| 57                                     | 0.000063  |
| 58                                     | <0.000010 |
| 59                                     | 0.000203  |
| 60                                     | <0.000010 |
| 61                                     | 0.000091  |
| 62                                     | <0.000010 |
| 63                                     | <0.000010 |
| 64                                     | <0.000010 |
| 65                                     | <0.000010 |
| 66                                     | <0.000010 |
| 67                                     | <0.000010 |
| 68                                     | 0.000012  |
| 69                                     | 0.001157  |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 70                                     | 0.003964  |
| 71                                     | 0.00001   |
| 72                                     | <0.000010 |
| 73                                     | <0.000010 |
| 74                                     | 0.000029  |
| 75                                     | <0.000010 |
| 76                                     | 0.000196  |
| 77                                     | 0.000213  |
| 78                                     | <0.000010 |
| 79                                     | <0.000010 |
| 80                                     | <0.000010 |
| 81                                     | <0.000010 |
| 82                                     | 0.000328  |
| 83                                     | 0.000071  |
| 84                                     | 0.000123  |
| 85                                     | 0.000391  |
| 86                                     | 0.000498  |
| 87                                     | 0.000618  |
| 88                                     | 0.000672  |
| 89                                     | 0.000073  |
| 90                                     | 0.000013  |
| 91                                     | 0.000487  |
| 92                                     | 0.000128  |
| 93                                     | 0.003461  |
| 94                                     | 0.000678  |
| 95                                     | 0.000014  |
| 96                                     | 0.000014  |
| 97                                     | 0.000017  |
| 98                                     | <0.000010 |
| 99                                     | 0.000233  |
| 100                                    | <0.000010 |
| 101                                    | 0.000021  |
| 102                                    | 0.000094  |
| 103                                    | <0.000010 |
| 104                                    | 0.000016  |
| 105                                    | <0.000010 |
| 106                                    | 0.000895  |
| 107                                    | 0.000035  |
| 108                                    | <0.000010 |
| 109                                    | 0.000127  |
| 110                                    | 0.000557  |
| 111                                    | <0.000010 |
| 112                                    | <0.000010 |
| 113                                    | <0.000010 |
| 114                                    | <0.000010 |
| 115                                    | <0.000010 |
| 116                                    | <0.000010 |
| 117                                    | <0.000010 |
| 118                                    | <0.000010 |
| 119                                    | <0.000010 |
| 120                                    | <0.000010 |
| 121                                    | <0.000010 |
| 122                                    | <0.000010 |
| 123                                    | <0.000010 |
| 124                                    | <0.000010 |
| 125                                    | <0.000010 |
| 126                                    | <0.000010 |
| 127                                    | <0.000010 |
| 128                                    | <0.000010 |
| 129                                    | 0.000002  |
| 130                                    | <0.000010 |
| 131                                    | <0.000010 |
| 132                                    | <0.000010 |
| 133                                    | <0.000010 |
| 134                                    | <0.000010 |
| 135                                    | <0.000010 |
| 136                                    | <0.000010 |
| 137                                    | <0.000010 |
| 138                                    | <0.000010 |
| 139                                    | <0.000010 |
| 140                                    | <0.000010 |
| 141                                    | <0.000010 |
| 142                                    | 0.00013   |
| 143                                    | <0.000010 |
| 144                                    | <0.000010 |
| 145                                    | <0.000010 |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 146                                    | <0.000010 |
| 147                                    | <0.000010 |
| 148                                    | <0.000010 |
| 149                                    | <0.000010 |
| 150                                    | <0.000010 |
| 151                                    | 0.000017  |
| 152                                    | <0.000010 |
| 153                                    | <0.000010 |
| 154                                    | <0.000010 |
| 155                                    | 0.000059  |
| 156                                    | <0.000010 |
| 157                                    | <0.000010 |
| 158                                    | <0.000010 |
| 159                                    | <0.000010 |
| 160                                    | <0.000010 |
| 161                                    | <0.000010 |
| 162                                    | <0.000010 |
| 163                                    | <0.000010 |
| 164                                    | <0.000010 |
| 165                                    | <0.000010 |
| 166                                    | <0.000010 |
| 167                                    | <0.000010 |
| 168                                    | <0.000010 |
| 169                                    | 0.000021  |
| 170                                    | 0.000022  |
| 171                                    | <0.000010 |
| 172                                    | <0.000010 |
| 173                                    | <0.000010 |
| 174                                    | <0.000010 |
| 175                                    | 0.000119  |
| 176                                    | 0.000023  |
| 177                                    | 0.000111  |
| 178                                    | 0.000076  |
| 179                                    | <0.000010 |
| 180                                    | <0.000010 |
| 181                                    | 0.000017  |
| 182                                    | 0.000068  |
| 183                                    | <0.000010 |
| 184                                    | <0.000010 |
| 185                                    | 0.000022  |
| 186                                    | 0.000047  |
| 187                                    | 0.00008   |
| 188                                    | <0.000010 |
| 189                                    | 0.000018  |
| 190                                    | 0.000026  |
| 191                                    | <0.000010 |
| 192                                    | <0.000010 |
| 193                                    | <0.000010 |
| 194                                    | <0.000010 |
| 195                                    | <0.000010 |
| 196                                    | <0.000010 |
| 197                                    | <0.000010 |
| 198                                    | <0.000010 |
| 199                                    | <0.000010 |
| 200                                    | <0.000010 |
| 201                                    | 0.000014  |
| 202                                    | <0.000010 |
| 203                                    | <0.000010 |
| 204                                    | <0.000010 |
| 205                                    | <0.000010 |
| 206                                    | 0.000036  |
| 207                                    | 0.00003   |
| 208                                    | 0.000104  |
| 209                                    | <0.000010 |
| 210                                    | 0.000011  |
| 211                                    | 0.000058  |
| 212                                    | 0.0001330 |
| 213                                    | <0.000010 |
| 214                                    | <0.000010 |
| 215                                    | <0.000010 |
| 216                                    | <0.000010 |
| 217                                    | <0.000010 |
| 218                                    | 0.000013  |
| 219                                    | 0.001192  |
| 220                                    | 0.000988  |
| 221                                    | 0.000049  |



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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 222                                    | 0.000938  |
| 223                                    | 0.000053  |
| 224                                    | <0.000010 |
| 225                                    | 0.000196  |
| 226                                    | 0.000139  |
| 227                                    | <0.000010 |
| 228                                    | 0.026761  |
| 229                                    | 0.002109  |
| 230                                    | 0.000031  |
| 231                                    | 0.000770  |
| 232                                    | 0.001631  |
| 233                                    | 0.001654  |
| 234                                    | 0.000115  |
| 235                                    | 0.000023  |
| 236                                    | 0.000033  |
| 237                                    | 0.000024  |
| 238                                    | <0.000010 |
| 239                                    | 0.000026  |
| 240                                    | <0.000010 |
| 241                                    | <0.000010 |
| 242                                    | 0.000057  |
| 243                                    | 0.000546  |
| 244                                    | 0.000281  |
| 245                                    | 0.000015  |
| 246                                    | 0.000144  |
| 247                                    | 0.000019  |
| 248                                    | 0.000029  |
| 250                                    | 0.000412  |
| 251                                    | 0.000571  |
| 252                                    | <0.000010 |
| 253                                    | 0.000052  |
| 254                                    | <0.000010 |
| 255                                    | <0.000010 |
| 256                                    | <0.000010 |
| 257                                    | 0.000052  |
| 258                                    | <0.000010 |
| 259                                    | <0.000010 |
| 260                                    | 0.000016  |
| 261                                    | 0.000134  |
| 262                                    | <0.000010 |
| 263                                    | 0.000156  |
| 264                                    | 0.000036  |
| 265                                    | <0.000010 |
| 266                                    | <0.000010 |
| 267                                    | 0.000035  |
| 268                                    | <0.000010 |
| 269                                    | 0.000016  |
| 270                                    | <0.000010 |
| 271                                    | 0.000039  |
| 272                                    | 0.000031  |
| 273                                    | 0.000035  |
| 274                                    | 0.000040  |
| 275                                    | <0.000010 |
| 276                                    | <0.000010 |
| 277                                    | <0.000010 |
| 278                                    | 0.000252  |
| 279                                    | 0.000035  |
| 280                                    | 0.000071  |
| 281                                    | 0.000145  |
| 282                                    | <0.000010 |
| 283                                    | <0.000010 |
| 284                                    | 0.000024  |
| 285                                    | <0.000010 |
| 286                                    | <0.000010 |
| 287                                    | 0.000081  |
| 288                                    | 0.000251  |
| 289                                    | 0.000090  |
| 290                                    | <0.000010 |
| 291                                    | <0.000010 |
| 292                                    | 0.000190  |
| 293                                    | 0.000093  |
| 294                                    | 0.000046  |
| 295                                    | <0.000010 |
| 296                                    | 0.000512  |
| 297                                    | 0.000174  |
| 298                                    | <0.000010 |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |            |
|--|------------|
| EXAMPLE #                              | $K_i$      |
| 299                                    | 0.000039   |
| 300                                    | 0.001627   |
| 301                                    | 0.002065   |
| 302                                    | 0.000332   |
| 303                                    | 0.000044   |
| 304                                    | nd         |
| 305                                    | 0.000033   |
| 306                                    | 0.002067   |
| 307                                    | 0.000130   |
| 308                                    | 0.000141   |
| 309                                    | 0.000023   |
| 310                                    | 0.000165   |
| 311                                    | <0.000010  |
| 312                                    | <0.000010  |
| 313                                    | 0.001102   |
| 314                                    | 0.000042   |
| 315                                    | 0.000052   |
| 316                                    | 0.000601   |
| 317                                    | <0.000010  |
| 318                                    | <0.000010  |
| 319                                    | <0.000010  |
| 320                                    | <0.000010  |
| 321                                    | <0.000010  |
| 322                                    | <0.000010  |
| 323                                    | 0.000104   |
| 324                                    | <0.000010  |
| 325                                    | <0.000010  |
| 326                                    | <0.000010  |
| 327                                    | <0.000010  |
| 328                                    | <0.000010  |
| 329                                    | 0.000030   |
| 330                                    | <0.000010  |
| 331                                    | 0.001086   |
| 332                                    | 0.000621   |
| 333                                    | 0.000511   |
| 334                                    | 0.000572   |
| 335                                    | 0.000150   |
| 336                                    | 0.000198   |
| 337                                    | <0.000010  |
| 338                                    | 0.000013   |
| 339                                    | 0.000036   |
| 340                                    | <0.000010  |
| 341                                    | <0.000010  |
| 342                                    | <0.000010  |
| 343                                    | <0.000010  |
| 344                                    | <0.000010  |
| 345                                    | <0.000010  |
| 346                                    | 0.000042   |
| 347                                    | 0.000013   |
| 348                                    | 0.000034   |
| 349                                    | 0.000023   |
| 350                                    | <0.000010  |
| 351                                    | <0.000010  |
| 352                                    | 0.000014   |
| 353                                    | <0.000010  |
| 354                                    | 0.000010   |
| 355                                    | 0.000014   |
| 356                                    | 0.000039   |
| 357                                    | <0.000010  |
| 358                                    | <0.000010  |
| 359                                    | <0.000010  |
| 360                                    | <0.000010  |
| 361                                    | <0.000010  |
| 362                                    | 0.000016   |
| 363                                    | 0.000017   |
| 364                                    | <0.000010  |
| 365                                    | <0.000010  |
| 366                                    | 0.000024   |
| 367                                    | nd         |
| 368                                    | nd         |
| 369                                    | <0.000010  |
| 370                                    | 0.000285   |
| 371                                    | <0.0000010 |
| 372                                    | nd         |
| 373                                    | <0.0000010 |
| 374                                    | <0.0000010 |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |            |
|--|------------|
| EXAMPLE #                              | $K_i$      |
| 375                                    | 0.00010999 |
| 376                                    | <0.0000010 |
| 377                                    | <0.0000010 |
| 378                                    | <0.0000010 |

nd = not determined

The inhibition constant ( $K_i$ ) is the dissociation constant of an enzyme-inhibitor complex or a protein/small molecule complex, wherein the small molecule is inhibiting binding of one protein to another protein or peptide. So a large  $K_i$  value indicates a low binding affinity and a small  $K_i$  value indicates a high binding affinity.

TABLE 2 shows inhibition constants for the inhibition of a Bak BH3 peptide probe to Bcl-2 protein and indicate that compounds according to the invention have high binding affinities for anti-apoptotic Bcl-2 protein. The compounds are therefore expected to have utility in treatment of diseases during which anti-apoptotic Bcl-2 protein is expressed.

## RS4;11 Cell Viability Assay

The acute lymphoblastic leukemia (ALL) cell line RS4;11 was used as the primary human cell line to assess the cellular activity of Bcl-2 selective agents in vitro and their efficacy in vivo. Previous studies have shown by BH3 profiling, a mitochondrial assay that classifies blocks in the intrinsic apoptotic pathway, that RS4;11 cells were highly dependant on BCL-2 for survival and sensitive to the Bcl-2 family member inhibitor ABT-737 (Blood, 2008, Vol. 111, 2300-2309). The prevalence of Bcl-2 complexed to the proapoptotic BH3 protein Bim in RS4;11 suggests that these cells are "primed" or more susceptible to cell death by antagonism of the antiapoptotic protein Bcl-2 for which they depend on for survival.

RS4;11 cells were cultured in RPMI-1640 supplemented with 2 mM L-glutamine, 10% FBS, 1 mM sodium pyruvate, 2 mM HEPES, 1% penicillin/streptomycin (Invitrogen), 4.5 g/L glucose and maintained at 37 C containing 5% CO<sub>2</sub>. To test for the cellular activity of compounds in vitro, cells were treated at 50,000 cells per well in 96-well microtiter plates in the presence of 10% human serum for 48 hours in a humidified chamber with 5% CO<sub>2</sub>. Cell cytotoxicity EC<sub>50</sub> values were assessed using CellTiter Glo (Promega) according to the manufacturer's recommendations. The EC<sub>50</sub> values were determined as a percentage of viable cells following treatment compared to the untreated control cells.

TABLE 3

| RS4; 11 EC <sub>50</sub> Values ( $\mu$ M) |         |
|--|---------|
| EXAMPLE #                                  | EC50    |
| 1  | 0.712   |
| 2  | 0.783   |
| 3  | 0.0142  |
| 4  | 0.01854 |
| 5  | 0.01241 |
| 6  | 0.03487 |
| 7  | 0.192   |
| 8  | 0.158   |
| 9  | 0.01476 |
| 10   | 0.05202 |
| 11   | 0.01393 |
| 12   | 0.03471 |
| 13   | 0.0232  |

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TABLE 3-continued

| RS4; 11 EC <sub>50</sub> Values ( $\mu$ M) |         |
|--|---------|
| EXAMPLE #                                  | EC50    |
| 14   | 3.8947  |
| 15   | 0.01276 |
| 16   | 1.2098  |
| 17   | 0.475   |
| 18   | 0.086   |
| 19   | 0.465   |
| 20   | 0.191   |
| 21   | 0.062   |
| 22   | 0.085   |
| 23   | 0.045   |
| 24   | 0.00983 |
| 25   | 0.007   |
| 26   | 0.05888 |
| 27   | 0.33237 |
| 28   | 0.0419  |
| 29   | 0.02047 |
| 30   | 0.01529 |
| 31   | 0.01565 |
| 32   | 0.08147 |
| 33   | 0.00711 |
| 34   | 0.00748 |
| 35   | 0.29147 |
| 36   | 0.18137 |
| 37   | 0.00118 |
| 38   | 3.5092  |
| 39   | 0.01974 |
| 40   | 0.09974 |
| 41   | 0.05801 |
| 42   | 0.53412 |
| 43   | 0.27208 |
| 44   | 0.05309 |
| 45   | 0.00992 |
| 46   | >5      |
| 47   | 0.03265 |
| 48   | 0.00333 |
| 49   | 0.35161 |
| 50   | 0.31264 |
| 51   | 0.02308 |
| 52   | 0.19964 |
| 53   | 0.06674 |
| 54   | 1.9158  |
| 55   | 0.0132  |
| 56   | 0.08654 |
| 57   | 0.42611 |
| 58   | >5      |
| 59   | 0.7215  |
| 60   | 0.05948 |
| 61   | 0.18337 |
| 62   | 0.02506 |
| 63   | 0.00751 |
| 64   | 0.00025 |
| 65   | 0.00025 |
| 66   | 0.01893 |
| 67   | 0.04954 |
| 68   | 0.10846 |
| 69   | 1.7243  |
| 70   | >5      |
| 71   | 0.09165 |
| 72   | 0.00751 |
| 73   | 0.02369 |
| 74   | 0.057   |
| 75   | 0.01509 |
| 76   | 0.51131 |
| 77   | 0.76196 |
| 78   | 0.01252 |
| 79   | 0.0649  |
| 80   | 0.06863 |
| 81   | 0.04814 |
| 82   | 0.68383 |
| 83   | 0.197   |
| 84   | 0.158   |
| 85   | 1.95    |
| 86   | 1.02    |
| 87   | 1.18    |
| 88   | 0.447   |
| 89   | 0.06446 |

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TABLE 3-continued

| RS4; 11 EC <sub>50</sub> Values (μM) |         |
|--------------------------------------|---------|
| EXAMPLE #                            | EC50    |
| 90                                   | 0.06299 |
| 91                                   | 0.18296 |
| 92                                   | 0.08089 |
| 93                                   | >5      |
| 94                                   | 1.6946  |
| 95                                   | 0.02954 |
| 96                                   | 0.04356 |
| 97                                   | 0.05557 |
| 98                                   | 0.0229  |
| 99                                   | 1.3923  |
| 100                                  | 0.13666 |
| 101                                  | 0.2991  |
| 102                                  | 0.62178 |
| 103                                  | 0.03917 |
| 104                                  | 0.07125 |
| 105                                  | 0.05357 |
| 106                                  | 0.82639 |
| 107                                  | 0.06117 |
| 108                                  | 0.02407 |
| 109                                  | 0.18339 |
| 110                                  | 0.53638 |
| 111                                  | 0.01451 |
| 112                                  | 0.02063 |
| 113                                  | 0.00136 |
| 114                                  | 0.01078 |
| 115                                  | 0.01184 |
| 116                                  | 0.02853 |
| 117                                  | 0.0182  |
| 118                                  | 0.01294 |
| 119                                  | 0.01138 |
| 120                                  | 0.00147 |
| 121                                  | 0.05972 |
| 122                                  | 0.00185 |
| 123                                  | 0.00333 |
| 124                                  | 0.21224 |
| 125                                  | 0.00838 |
| 126                                  | 0.05359 |
| 127                                  | 0.00975 |
| 128                                  | 0.00589 |
| 129                                  | 0.01484 |
| 130                                  | 0.01059 |
| 131                                  | 0.01266 |
| 132                                  | 0.02209 |
| 133                                  | 0.03186 |
| 134                                  | 0.00251 |
| 135                                  | 0.00237 |
| 136                                  | 0.00296 |
| 137                                  | 0.01272 |
| 138                                  | 0.00152 |
| 139                                  | 0.01681 |
| 140                                  | 0.01275 |
| 141                                  | 0.02044 |
| 142                                  | 0.34531 |
| 143                                  | 0.01914 |
| 144                                  | 0.0212  |
| 145                                  | 0.004   |
| 146                                  | 0.01916 |
| 147                                  | 0.02618 |
| 148                                  | 0.00938 |
| 149                                  | 0.01347 |
| 150                                  | 0.05103 |
| 151                                  | 0.03372 |
| 152                                  | 0.02037 |
| 153                                  | 0.01723 |
| 154                                  | 0.02647 |
| 155                                  | 0.59421 |
| 156                                  | 0.00805 |
| 157                                  | 0.01086 |
| 158                                  | 0.01793 |
| 159                                  | 0.01179 |
| 160                                  | 0.08363 |
| 161                                  | 0.03465 |
| 162                                  | 0.01297 |
| 163                                  | 0.00432 |
| 164                                  | 0.01476 |
| 165                                  | 0.0051  |

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TABLE 3-continued

| RS4; 11 EC <sub>50</sub> Values (μM) |            |
|--------------------------------------|------------|
| EXAMPLE #                            | EC50       |
| 166                                  | 0.01185    |
| 167                                  | 0.00093    |
| 168                                  | 0.08867    |
| 169                                  | 0.07626    |
| 170                                  | 0.12515    |
| 171                                  | 0.05272    |
| 172                                  | 0.02053    |
| 173                                  | 0.00516    |
| 174                                  | 0.12621    |
| 175                                  | >1         |
| 176                                  | 0.13353    |
| 177                                  | 0.15936    |
| 178                                  | 0.20234    |
| 179                                  | 0.04273    |
| 180                                  | 0.0118     |
| 181                                  | 0.10612    |
| 182                                  | 0.1234     |
| 183                                  | 0.01753    |
| 184                                  | 0.02323    |
| 185                                  | 0.02747    |
| 186                                  | 0.06443    |
| 187                                  | 0.21494    |
| 188                                  | 0.01638    |
| 189                                  | 0.14397    |
| 190                                  | 0.55068    |
| 191                                  | 0.00691    |
| 192                                  | 0.00241    |
| 193                                  | 0.00076    |
| 194                                  | 0.00819    |
| 195                                  | 0.00207    |
| 196                                  | 0.00172    |
| 197                                  | 0.0125     |
| 198                                  | 0.03619    |
| 199                                  | 0.00506    |
| 200                                  | 0.01099    |
| 201                                  | 0.59132    |
| 202                                  | 0.0438     |
| 203                                  | 0.02208    |
| 204                                  | 0.16475    |
| 205                                  | 0.01059    |
| 206                                  | 0.05291    |
| 207                                  | 0.00376    |
| 208                                  | 0.12121    |
| 209                                  | 0.0045     |
| 210                                  | 0.06022    |
| 211                                  | 0.3073     |
| 212                                  | 0.01283    |
| 213                                  | 0.0060976  |
| 214                                  | 0.0043751  |
| 215                                  | 0.00056038 |
| 216                                  | 0.68263    |
| 217                                  | 0.0015528  |
| 218                                  | 0.0072907  |
| 219                                  | >1         |
| 220                                  | >1         |
| 221                                  | 0.094771   |
| 222                                  | >1         |
| 223                                  | 0.18208    |
| 224                                  | 0.013887   |
| 225                                  | 0.56001    |
| 226                                  | 0.1178     |
| 227                                  | 0.0073566  |
| 228                                  | >1         |
| 229                                  | >1         |
| 230                                  | 0.052821   |
| 231                                  | 0.52301    |
| 232                                  | >1         |
| 233                                  | >1         |
| 234                                  | 0.13532    |
| 235                                  | 0.03232    |
| 236                                  | 0.04292    |
| 237                                  | 0.05316    |
| 238                                  | 0.10303    |
| 239                                  | 0.023699   |
| 240                                  | 0.017266   |
| 241                                  | 0.11377    |

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TABLE 3-continued

| RS4; 11 EC <sub>50</sub> Values (μM) |            |
|--------------------------------------|------------|
| EXAMPLE #                            | EC50       |
| 242                                  | 0.22275    |
| 243                                  | 0.80718    |
| 244                                  | 0.79378    |
| 245                                  | 0.083614   |
| 246                                  | 0.40218    |
| 247                                  | 0.092976   |
| 248                                  | 0.099588   |
| 250                                  | >1         |
| 251                                  | 0.91782    |
| 252                                  | 0.003475   |
| 253                                  | 0.049586   |
| 254                                  | 0.019908   |
| 255                                  | 0.009004   |
| 256                                  | 0.017997   |
| 257                                  | 0.026002   |
| 258                                  | 0.00055345 |
| 259                                  | 0.00038795 |
| 260                                  | 0.0054323  |
| 261                                  | 0.18366    |
| 262                                  | 0.016346   |
| 263                                  | >1         |
| 264                                  | 0.68866    |
| 265                                  | 0.0071718  |
| 266                                  | 0.0072924  |
| 267                                  | 0.06944    |
| 268                                  | 0.048792   |
| 269                                  | 0.0072346  |
| 270                                  | 0.0025216  |
| 271                                  | 0.43657    |
| 272                                  | 0.84006    |
| 273                                  | 0.20925    |
| 274                                  | 0.21418    |
| 275                                  | 0.14303    |
| 276                                  | 0.0035006  |
| 277                                  | 0.0081845  |
| 278                                  | 0.79393    |
| 279                                  | 0.22492    |
| 280                                  | 0.45923    |
| 281                                  | 0.65371    |
| 282                                  | 0.032187   |
| 283                                  | 0.013096   |
| 284                                  | 0.16213    |
| 285                                  | 0.057413   |
| 286                                  | 0.034464   |
| 287                                  | 0.59312    |
| 288                                  | 0.39042    |
| 289                                  | 0.6687     |
| 290                                  | 0.10663    |
| 291                                  | 0.016079   |
| 292                                  | 0.88938    |
| 293                                  | 0.28715    |
| 294                                  | 0.12525    |
| 295                                  | 0.014803   |
| 296                                  | 0.76869    |
| 297                                  | 0.59157    |
| 298                                  | 0.070305   |
| 299                                  | 0.067981   |
| 300                                  | 0.76334    |
| 301                                  | >1         |
| 302                                  | 0.38106    |
| 303                                  | 0.04776    |
| 304                                  | 0.29755    |
| 305                                  | 0.032539   |
| 306                                  | 0.55348    |
| 307                                  | 0.12767    |
| 308                                  | 0.257      |
| 309                                  | 0.052421   |
| 310                                  | >1         |
| 311                                  | 0.035835   |
| 312                                  | 0.016178   |
| 313                                  | >1         |
| 314                                  | 0.66006    |
| 315                                  | 0.21027    |
| 316                                  | >1         |
| 317                                  | 0.013313   |
| 318                                  | 0.011566   |

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TABLE 3-continued

| RS4; 11 EC <sub>50</sub> Values (μM) |            |
|--------------------------------------|------------|
| EXAMPLE #                            | EC50       |
| 319                                  | 0.0044972  |
| 320                                  | 0.050974   |
| 321                                  | 0.0188     |
| 322                                  | 0.012367   |
| 323                                  | 0.71689    |
| 324                                  | 0.0045254  |
| 325                                  | 0.012319   |
| 326                                  | 0.023133   |
| 327                                  | 0.0027224  |
| 328                                  | 0.0098808  |
| 329                                  | 0.42369    |
| 330                                  | 0.0097843  |
| 331                                  | 0.92638    |
| 332                                  | 0.45738    |
| 333                                  | 0.46292    |
| 334                                  | >1         |
| 335                                  | 0.26951    |
| 336                                  | 0.35134    |
| 337                                  | 0.001759   |
| 338                                  | 0.003399   |
| 339                                  | 0.45016    |
| 340                                  | 0.05646    |
| 341                                  | 0.031652   |
| 342                                  | 0.050891   |
| 343                                  | 0.12664    |
| 344                                  | 0.0066616  |
| 345                                  | 0.0092536  |
| 346                                  | 0.19003    |
| 347                                  | 0.018849   |
| 348                                  | 0.050263   |
| 349                                  | 0.023086   |
| 350                                  | 0.0058378  |
| 351                                  | 0.0020618  |
| 352                                  | 0.0011961  |
| 353                                  | 0.0050512  |
| 354                                  | 0.053231   |
| 355                                  | 0.018771   |
| 356                                  | 0.026623   |
| 357                                  | 0.013235   |
| 358                                  | 0.0038131  |
| 359                                  | 0.0059243  |
| 360                                  | 0.0098968  |
| 361                                  | 0.00053755 |
| 362                                  | 0.031726   |
| 363                                  | 0.02643    |
| 364                                  | 0.011244   |
| 365                                  | 0.0030168  |
| 366                                  | 0.016548   |
| 367                                  | nd         |
| 368                                  | nd         |
| 369                                  | 0.0079974  |
| 370                                  | nd         |
| 371                                  | 0.007165   |
| 372                                  | nd         |
| 373                                  | nd         |
| 374                                  | 0.015475   |
| 375                                  | 0.56013    |
| 376                                  | 0.008765   |
| 377                                  | 0.002377   |
| 378                                  | 0.006764   |

55 nd = not determined

TABLE 3 shows the utility of compounds having Formula I to functionally inhibit anti-apoptotic Bcl-2 protein in a cellular context. The acute lymphoblastic leukemia (ALL) cell line RS4;11 has been shown by BH3 profiling, a mitochondrial assay that classifies blocks in the intrinsic apoptotic pathway, to be highly dependant on Bcl-2 for survival and is sensitive to the Bcl-2 family member inhibitor ABT-737 (*Blood*, 2008, Vol. 111, 2300-2309). The ability of compounds to kill RS4;11 cells is a direct measure of the compounds ability to inhibit anti-apoptotic Bcl-2 protein function. Compounds of Formula I are very effective in killing RS4;11 cells as demonstrated by low EC<sub>50</sub> values.



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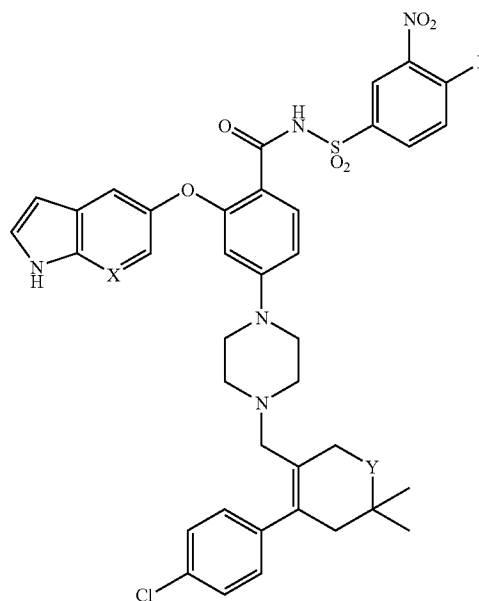
Compounds taught in U.S. patent application Ser. No. 12/631,404, entitled "BCL-2-SELECTIVE APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE DISEASES," filed on Dec. 4, 2009, have utility for the treatment of various cancers and autoimmune diseases due to their activity against Bcl-2 family proteins, and more specifically Bcl-2. These compounds bind to Bcl-2 with high affinity in a FRET based assay described in Ser. No. 12/631,404. The administration of a one or more of these compounds to cells that are dependant on Bcl-2 or Bcl-2 family proteins for survival, such as the RS4;11 B-cell leukemia human tumor cell line, results in apoptosis, also known as programmed cell death. The amount of apoptosis caused by administration of the compound is represented by the EC50 in the cell viability assay, which is a measure of the number of living cells after administration of compound.

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TABLE 4 identifies certain compounds (described below in Examples in 19, 20, 23 and 92 and described more fully in Ser. No. 12/631,404, the disclosure of which is incorporated herein by reference) with the various substituents being defined by R, X and Y as set forth. As can be seen from TABLE 4, these compounds exhibit a trend of increasing binding affinity ( $K_i$ ) for Bcl-2 with increasing levels of apoptosis, or cell death, in the Bcl-2 dependant tumor cell line RS4;11. On this basis, the inventors expect that compounds with even greater affinity towards Bcl-2 than those compounds shown in Table 4 will exhibit a similar trend, potentially eliciting even greater levels of apoptosis, when administered to cells dependent on Bcl-2 for survival.

TABLE 4

Selected compounds in U.S. patent application Ser. No. 12/631,404



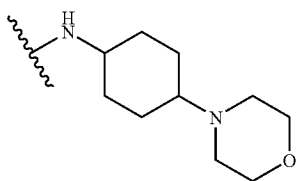
| EXAMPLE | R | X | Y | Bcl-2 FRET $K_i$ ( $\mu$ M) | RS4;11 EC50 ( $\mu$ M) |
|---------|---|---|---|-----------------------------|------------------------|
| (23)    |   | C | O | 0.000083                    | 0.045                  |
| (92)    |   | C | C | 0.000128                    | 0.081                  |
| (20)    |   | C | C | 0.000181                    | 0.191                  |

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TABLE 4-continued

|      |   |   |   |          |       |
|------|---|---|---|----------|-------|
| (19) |  | C | C | 0.000226 | 0.465 |
|------|---|---|---|----------|-------|

To this end, binding affinity and cellular activity for compounds according to the present invention were compared with structurally similar indole compounds. In particular, the compounds of the present invention, in which a nitrogen is contained at a specific position within the heteroarene fused to the heteroaryl ring were compared with the corresponding indole compounds, which latter compounds lack only the specific nitrogen substitution included in the compounds of the present invention.

As can be seen in TABLE 5, compounds of the present invention having the specific nitrogen substitutions shown (i.e., compounds of Examples 1, 2, 3, 4, 5, 6, 9, 10, 11, 12, 13, 15, 16, and 17, where Z=N) in fact achieve relatively greater levels of apoptosis when administered to cells that depend on Bcl-2 for survival and have increased affinity towards Bcl-2 relative to the corresponding structural analogs lacking the specific nitrogen substitution (i.e., compounds of Examples 87, 88, 89, 90, 91, 19, 20, 21, 92, 22, 23, 93, and 94, respectively, where Z=C, taught in 9696USL2, the disclosure of which is incorporated herein by reference).

Specifically, the seventh column of TABLE 5 compares binding affinity of compounds of the present invention (the compound identified by the designated substituents in the uppermost row in each pair of rows set apart by blank rows) to corresponding compounds lacking the described nitrogen substitution. In each comparison, compounds of the present application (upper row of each pair of rows separated by a blank row) bind Bcl-2 with greater affinity to Bcl-2 than the corresponding analogs (lower row of each pair of rows separated by a blank row).

Further, column 8 of TABLE 5 compares the amount of apoptosis in the Bcl-2 dependant RS4;11 cell line achieved using compounds of the present invention (again the compound identified by the designated substituents in the uppermost row in each pair of rows set apart by blank rows) to that achieved using compounds of Examples 87, 88, 89, 90, 91, 19, 20, 21, 92, 22, 23, 93, and 94, where Z=C. In each comparison, compounds of the present invention (upper row of each pair of rows separated by a blank row) achieve greater extent of apoptosis in Bcl-2 dependent RS4;11 cells than the corresponding analogs (lower row of each pair of rows separated by a blank row).

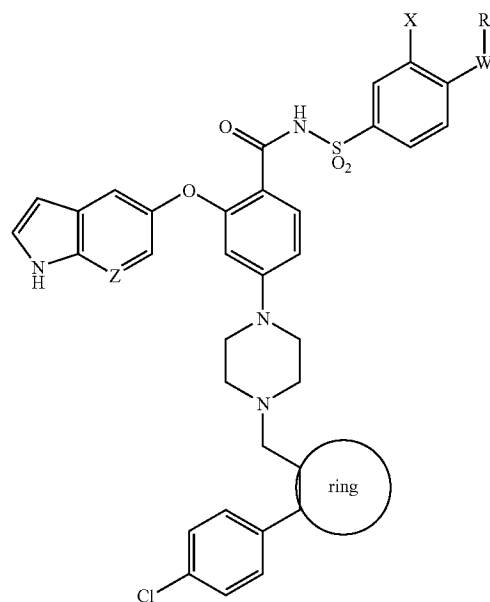
The increase in binding affinity between the compounds of the present invention and corresponding analogs ranges from 2.7× to greater than 100×, and the increased potency in RS4;11 cells ranges from a 1.65× increase to greater than 10× increase.

As detailed below, a specific substitution of a nitrogen atom for a carbon atom leads to unexpected increase in binding affinity to antiapoptotic Bcl-2 and increase in potency in cell viability assays assessing apoptosis in Bcl-2 dependent cell lines.

This invention therefore comprises a series of compounds that demonstrate unexpected properties with respect to their binding to and inhibiting the activity of anti-apoptotic Bcl-2 protein to a significantly greater extent than corresponding analog compounds.

TABLE 5

Direct comparison of compounds of the present invention with corresponding analogs.

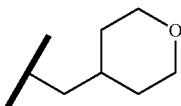
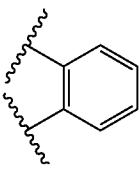
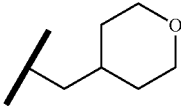
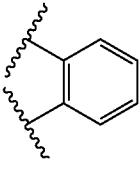
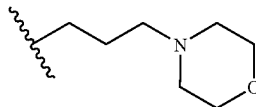
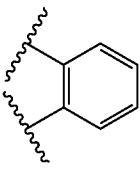
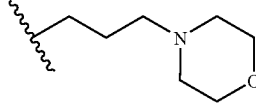
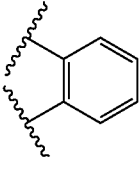
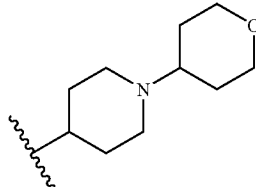
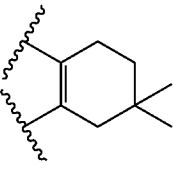
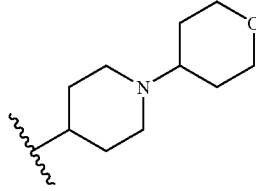
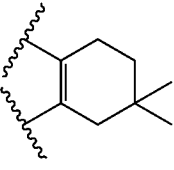
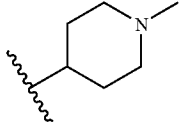
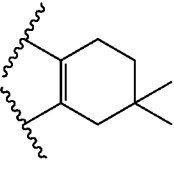
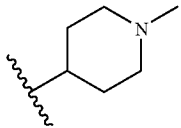
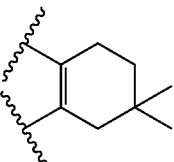


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TABLE 5-continued

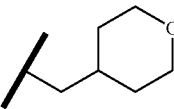
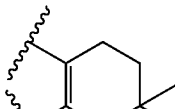
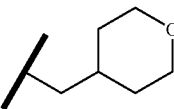
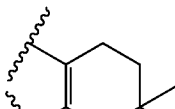
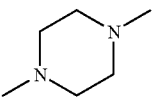
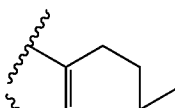
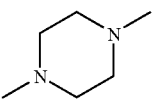
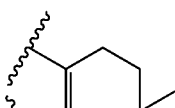
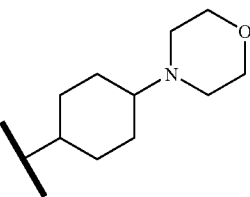
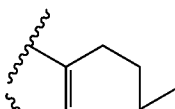
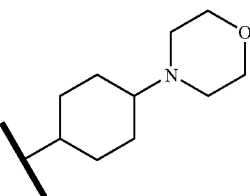
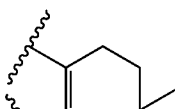
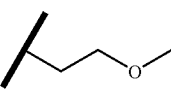
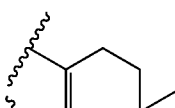
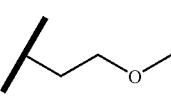
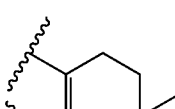
| EXAMPLE | R   | W  | X               | Ring  | Z | Bcl-2 FRET<br>ki (μM) | RS4;11<br>EC50 (μM) |
|---------|---|----|-----------------|---|---|-----------------------|---------------------|
| (1)     |    | NH | NO <sub>2</sub> |    | N | 0.000225              | 0.712               |
| (87)    |    | NH | NO <sub>2</sub> |    | C | 0.000618              | 1.180               |
| (2)     |    | NH | NO <sub>2</sub> |    | N | <0.000010             | 0.783               |
| (88)    |   | NH | NO <sub>2</sub> |   | C | 0.672                 | 0.447               |
| (3)     |  | NH | NO <sub>2</sub> |  | N | 0.000013              | 0.0142              |
| (89)    |  | NH | NO <sub>2</sub> |  | C | 0.000074              | 0.064               |
| (4)     |  | NH | NO <sub>2</sub> |  | N | <0.00001              | 0.019               |
| (90)    |  | NH | NO <sub>2</sub> |  | C | 0.000013              | 0.063               |

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TABLE 5-continued

|      |   |    |                 |   |   |          |       |
|------|---|----|-----------------|---|---|----------|-------|
| (5)  |    | NH | NO <sub>2</sub> |    | N | <0.00001 | 0.012 |
| (18) |    | NH | NO <sub>2</sub> |    | C | 0.000017 | 0.086 |
| (6)  |    | NH | NO <sub>2</sub> |    | N | 0.000018 | 0.035 |
| (91) |    | NH | NO <sub>2</sub> |    | C | 0.000487 | 0.183 |
| (9)  |  | NH | NO <sub>2</sub> |  | N | <0.00001 | 0.015 |
| (19) |  | NH | NO <sub>2</sub> |  | C | 0.000226 | 0.465 |
| (10) |  | NH | NO <sub>2</sub> |  | N | <0.00001 | 0.052 |
| (20) |  | NH | NO <sub>2</sub> |  | C | 0.000181 | 0.191 |

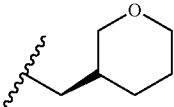
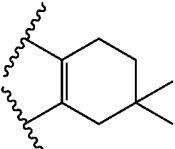
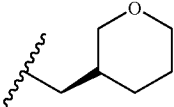
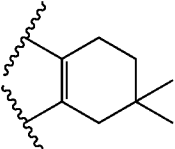
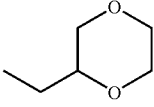
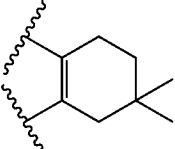
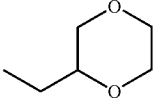
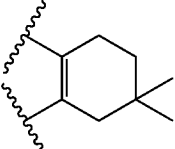
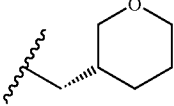
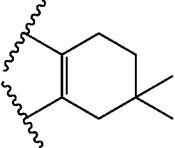
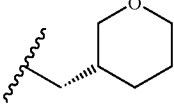
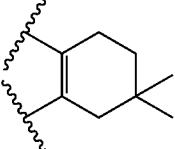
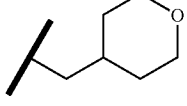
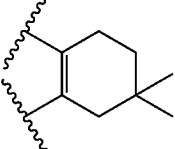
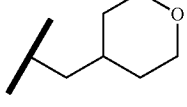
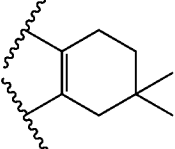
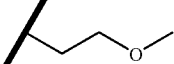
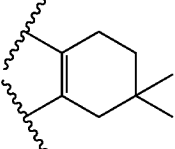


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TABLE 5-continued

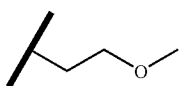
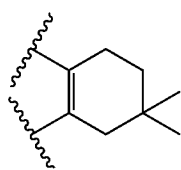
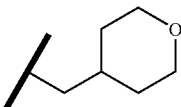
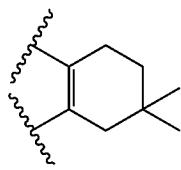
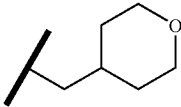
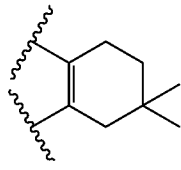
| (11) |    | NH NO <sub>2</sub>                 |    | N | 0.000016 | 0.014 |
|------|---|------------------------------------|---|---|----------|-------|
| (21) |    | NH NO <sub>2</sub>                 |    | C | 0.000912 | 0.062 |
| (12) |    | O NO <sub>2</sub>                  |    | N | <0.00001 | 0.035 |
| (92) |    | O NO <sub>2</sub>                  |    | C | 0.000128 | 0.081 |
| (13) |  | NH NO <sub>2</sub>                 |  | N | <0.00001 | 0.023 |
| (22) |  | NH NO <sub>2</sub>                 |  | C | 0.000291 | 0.085 |
| (15) |  | NH NO <sub>2</sub>                 |  | N | <0.00001 | 0.013 |
| (23) |  | NH NO <sub>2</sub>                 |  | C | 0.000083 | 0.045 |
| (16) |  | NH SO <sub>2</sub> CF <sub>3</sub> |  | N | 0.000219 | 1.210 |

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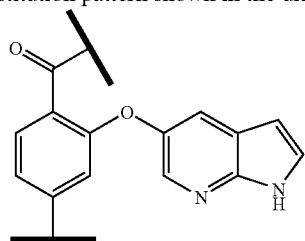
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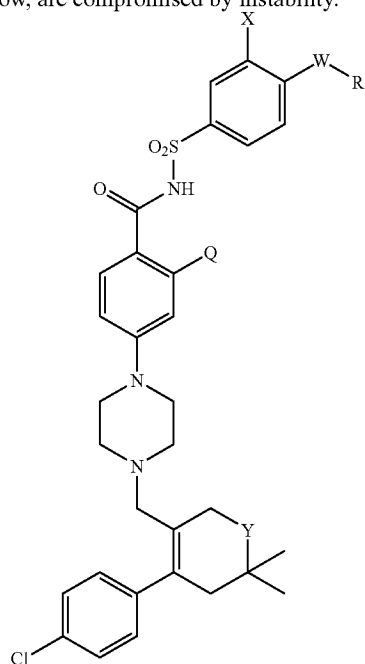
TABLE 5-continued

|      |   |                                    |   |   |          |        |
|------|---|------------------------------------|---|---|----------|--------|
| (93) |  | NH SO <sub>2</sub> CF <sub>3</sub> |  | C | 0.035    | >5.000 |
| (17) |  | NH SO <sub>2</sub> CF <sub>3</sub> |  | N | 0.000090 | 0.475  |
| (94) |  | NH SO <sub>2</sub> CF <sub>3</sub> |  | C | 0.000678 | 1.690  |

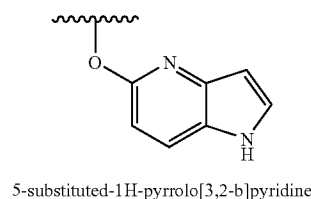
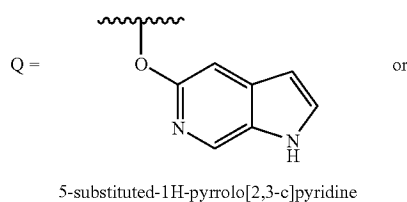
More specifically, compounds of the present invention contain a substitution pattern shown in the diagram below.



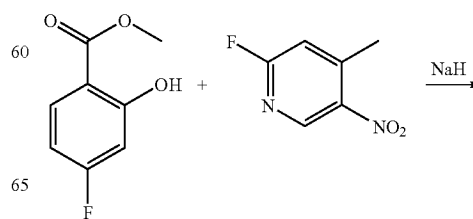
Other compounds that contain isomeric ring systems to that shown above, such as those rings systems containing a nitrogen adjacent to the oxygenated carbon within the ring, as shown below, are compromised by instability.



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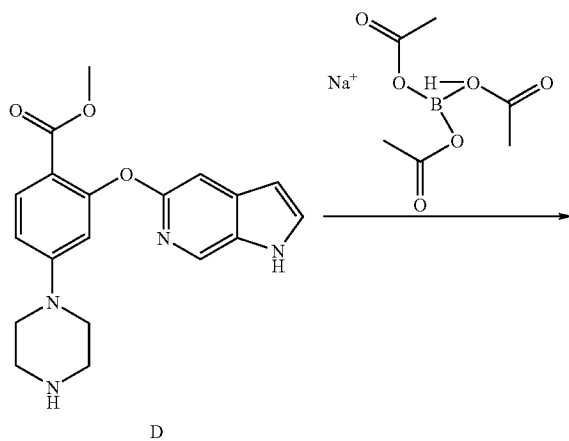
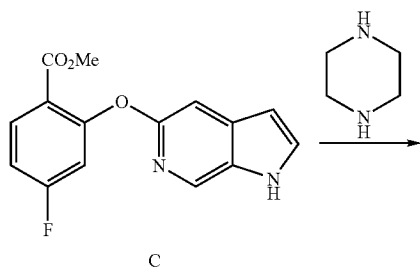
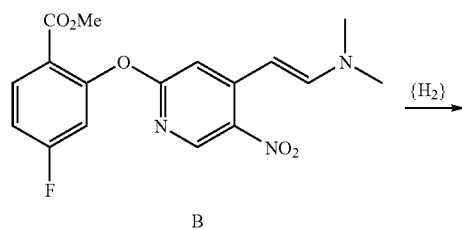
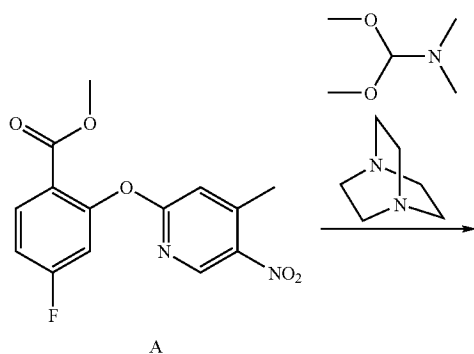
Specifically, this was discovered by the inventors in the following compound preparation. The intermediate structure F, that directly precedes the final product of the unstable compound, was prepared according to the route below. All intermediates A-F were stable and isolable using techniques known to those skilled in the art.



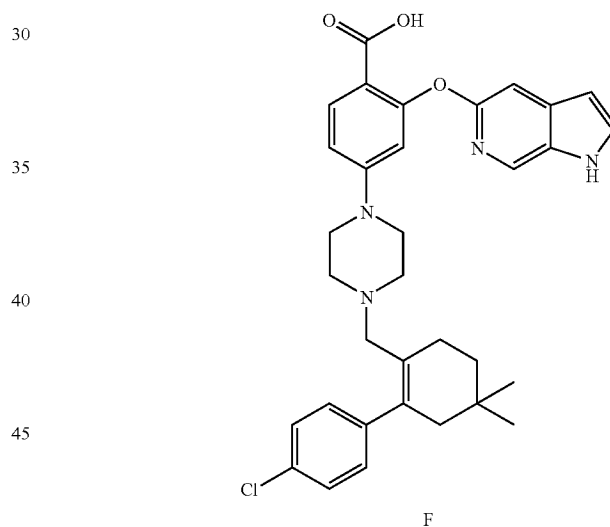
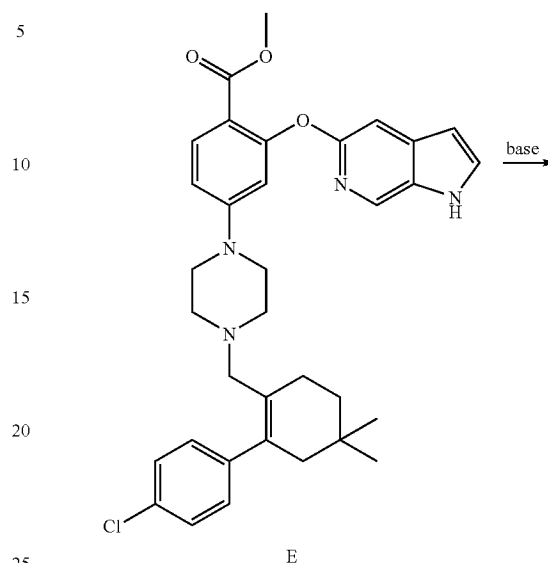
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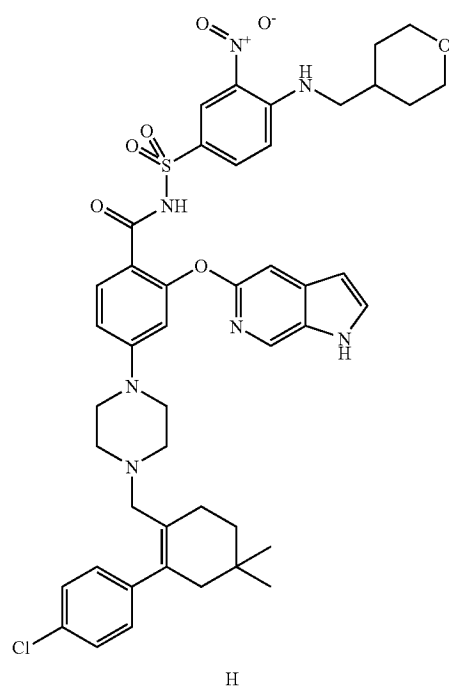
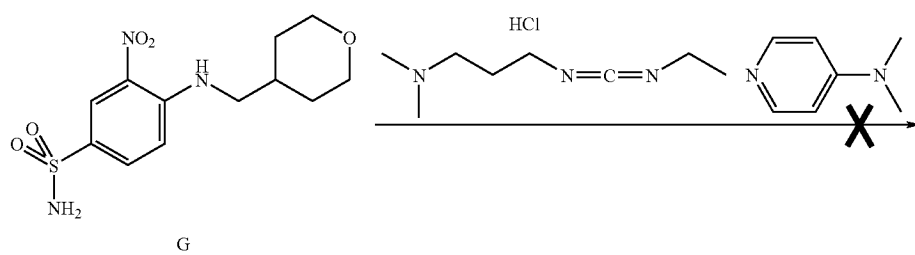
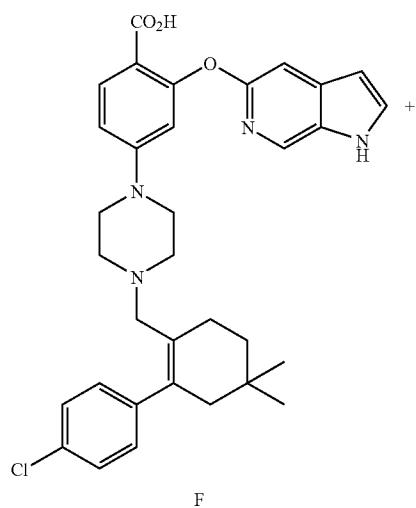


Intermediate F, shown in the scheme above, was reacted with intermediate G using standard coupling conditions that are known to those skilled in the art. The reaction mixture was analyzed via HPLC/MS to monitor the formation of a peak corresponding to the compound H. While this peak formed within hours of initiating the reaction below, the peak progressively disappeared during workup and chromatography, until it no longer was present. The lack of stability of the putative compound originates from the position of the nitrogen within the fused ring-system described above. This position, which is adjacent to the oxygen-bearing carbon in the 5-substituted-1H-pyrrolo[2,3-c]pyridine ring system shown below and described above, makes the compound H unstable.

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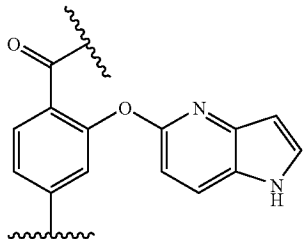




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It is expected that a compound containing the fused 5-substituted-1H-pyrrolo[3,2-b]pyridine ring system below would be similarly unstable, since the position of the nitrogen is adjacent to the oxygen-bearing carbon within the ring.



Therefore, compounds with the 5-substituted-1H-pyrrolo [2,3-b]pyridines are preferred over the isomeric compounds.

It is expected that, because compounds having Formula (I) bind to Bcl-2, they would also have utility as binders to anti-apoptotic proteins having close structural homology to Bcl-2, such as, for example, anti-apoptotic Bcl-X<sub>L</sub>, Bcl-w, Mcl-1 and Bfl-1/A1 proteins.

Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer spleen cancer, and the like is described in commonly-owned PCT US 2004/36770, published as WO 2005/049593, and PCT US 2004/37911, published as WO 2005/024636.

Involvement of Bcl-2 proteins in immune and autoimmune diseases is described in *Current Allergy and Asthma Reports* 2003, 3, 378-384; *British Journal of Haematology* 2000, 110 (3), 584-90; *Blood* 2000, 95(4), 1283-92; and *New England Journal of Medicine* 2004, 351(14), 1409-1418.

Involvement of Bcl-2 proteins in arthritis is disclosed in commonly-owned U.S. Provisional Patent Application Ser. No. 60/988,479.

Involvement of Bcl-2 proteins in bone marrow transplant rejection is disclosed in commonly-owned U.S. patent application Ser. No. 11/941,196.

Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system. Cancers include, but are not limited to, hematologic and solid tumor types such as acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer (including estrogen-receptor positive breast cancer), bronchogenic carcinoma, Burkitt's lymphoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia,

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esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, gastric carcinoma, germ cell testicular cancer, gestational trophoblastic disease, glioblastoma, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer (including small cell lung cancer and non-small cell lung cancer), lymphangioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (lymphoma, including diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, peripheral T-cell lymphoma, pinealoma, polycythemia vera, prostate cancer (including hormone-insensitive (refractory) prostate cancer), rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), stomach cancer, squamous cell carcinoma, synovium, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer, Wilms' tumor and the like.

It is also expected that compounds having Formula (I) would inhibit growth of cells expressing Bcl-2 proteins derived from a pediatric cancer or neoplasm including embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoid/rhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitt's lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal tumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer and the like.

Autoimmune disorders include acquired immunodeficiency disease syndrome (AIDS), autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, and thrombocytopenia, acute or chronic immune disease associated with organ transplantation, Addison's disease, allergic diseases, alopecia, alopecia areata, atheromatous disease/arteriosclerosis, atherosclerosis, arthritis (including osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis and reactive arthritis), autoimmune bullous disease, abetalipoproteinemia, acquired immunodeficiency-related diseases, acute immune disease associated with organ transplantation, acquired acrocyanosis, acute and chronic parasitic or infectious processes, acute pancreatitis, acute renal failure, acute rheumatic fever, acute transverse myelitis, adenocarcinomas, aerial ectopic beats, adult (acute) respiratory distress syndrome, AIDS dementia complex, alcoholic cirrhosis, alcohol-induced liver injury, alcohol-induced hepatitis, allergic conjunctivitis,

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allergic contact dermatitis, allergic rhinitis, allergy and asthma, allograft rejection, alpha-1-antitrypsin deficiency, Alzheimer's disease, amyotrophic lateral sclerosis, anemia, angina pectoris, ankylosing spondylitis associated lung disease, anterior horn cell degeneration, antibody mediated cytotoxicity, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, arthropathy, asthenia, asthma, ataxia, atopic allergy, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, atrophic autoimmune hypothyroidism, autoimmune haemolytic anaemia, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), autoimmune mediated hypoglycaemia, autoimmune neutropaenia, autoimmune thrombocytopenia, autoimmune thyroid disease, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bronchiolitis obliterans, bundle branch block, burns, cachexia, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chlamydia, choleosarcoma, chronic alcoholism, chronic active hepatitis, chronic fatigue syndrome, chronic immune disease associated with organ transplantation, chronic eosinophilic pneumonia, chronic inflammatory pathologies, chronic mucocutaneous candidiasis, chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal common varied immunodeficiency (common variable hypogammaglobulinaemia), conjunctivitis, connective tissue disease associated interstitial lung disease, contact dermatitis, Coombs positive haemolytic anaemia, cor pulmonale, Creutzfeldt-Jakob disease, cryptogenic autoimmune hepatitis, cryptogenic fibrosing alveolitis, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, Crohn's disease, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatitis scleroderma, dermatologic conditions, dermatomyositis/polyomyositis associated lung disease, diabetes, diabetic arteriosclerotic disease, diabetes mellitus, Diffuse Lewy body disease, dilated cardiomyopathy, dilated congestive cardiomyopathy, discoid lupus erythematosus, disorders of the basal ganglia, disseminated intravascular coagulation, Down's Syndrome in middle age, drug-induced interstitial lung disease, drug-induced hepatitis, drug-induced movement disorders induced by drugs which block CNS dopamine, receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, enteropathic synovitis, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hemophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, female infertility, fibrosis, fibrotic lung disease, fungal sepsis, gas gangrene, gastric ulcer, giant cell arteritis, glomerular nephritis, glomerulonephritides, Goodpasture's syndrome, goitrous autoimmune hypothyroidism (Hashimoto's disease), gouty arthritis, graft rejection of any organ or tissue, graft versus host disease, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, group B streptococci (GBS) infection, Grave's disease, haemosiderosis associated lung disease, hairy cell leukemia, hairy cell leukemia, Hallerorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hematopoietic malignancies (leukemia and lymphoma), hemolytic anemia, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, Henoch-Schoenlein

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purpura, Hepatitis A, Hepatitis B, Hepatitis C, HIV infection/HIV neuropathy, Hodgkin's disease, hypoparathyroidism, Huntington's chorea, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hyperthyroidism, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic leucopaenia, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia, idiosyncratic liver disease, infantile spinal muscular atrophy, infectious diseases, inflammation of the aorta, inflammatory bowel disease, insulin dependent diabetes mellitus, interstitial pneumonitis, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile pernicious anaemia, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, Kawasaki's disease, kidney transplant rejection, *legionella*, leishmaniasis, leprosy, lesions of the corticospinal system, linear IgA disease, lipidema, liver transplant rejection, Lyme disease, lymphedema, lymphocytic infiltrative lung disease, malaria, male infertility idiopathic or NOS, malignant histiocytosis, malignant melanoma, meningitis, meningococemia, microscopic vasculitis of the kidneys, migraine headache, mitochondrial multisystem disorder, mixed connective tissue disease, mixed connective tissue disease associated lung disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel Dejerine-Thomas Shi-Drager and Machado-Joseph), myalgic encephalitis/Royal Free Disease, myasthenia gravis, microscopic vasculitis of the kidneys, *mycobacterium avium* intracellulare, *mycobacterium tuberculosis*, myelodysplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, nephrotic syndrome, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, Non-alcoholic Steatohepatitis, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, organ transplant rejection, orchitis/epididymitis, orchitis/vasectomy reversal procedures, organomegaly, osteoarthritis, osteoporosis, ovarian failure, pancreas transplant rejection, parasitic diseases, parathyroid transplant rejection, Parkinson's disease, pelvic inflammatory disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, phacogenic uveitis, *pneumocystis carinii* pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiomyopathy syndrome, postinfectious interstitial lung disease, premature ovarian failure, primary biliary cirrhosis, primary sclerosing hepatitis, primary myxoedema, primary pulmonary hypertension, primary sclerosing cholangitis, primary vasculitis, Progressive supranuclear Palsy, psoriasis, psoriasis type 1, psoriasis type 2, psoriatic arthropathy, pulmonary hypertension secondary to connective tissue disease, pulmonary manifestation of polyarteritis nodosa, post-inflammatory interstitial lung disease, radiation fibrosis, radiation therapy, Raynaud's phenomenon and disease, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, Reiter's disease, renal disease NOS, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, rheumatoid arthritis associated interstitial lung disease, rheumatoid spondylitis, sarcoidosis, Schmidt's syndrome, scleroderma, senile chorea, Senile Dementia of Lewy body type, sepsis syndrome, septic shock, seronegative arthropathies, shock, sickle cell anemia, Sjögren's disease associated lung disease, Sjögren's syndrome, skin allograft rejection, skin changes syndrome, small

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bowel transplant rejection, sperm autoimmunity, multiple sclerosis (all subtypes), spinal ataxia, spinocerebellar degenerations, spondyloarthropathy, spondyloarthropathy, sporadic, polyglandular deficiency type I sporadic, polyglandular deficiency type II, Still's disease, streptococcal myositis, stroke, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, sympathetic ophthalmia, Syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic lupus erythematosus-associated lung disease, systemic sclerosis, systemic sclerosis-associated interstitial lung disease, T-cell or FAB ALL, Takayasu's disease/arteritis, Telangiectasia, Th2 Type and Th1 Type mediated diseases, thromboangitis obliterans, thrombocytopenia, thyroiditis, toxicity, toxic shock syndrome, transplants, trauma/hemorrhage, type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), type B insulin resistance with acanthosis nigricans, type III hypersensitivity reactions, type IV hypersensitivity, ulcerative colitic arthropathy, ulcerative colitis, unstable angina, uremia, urosepsis, urticaria, uveitis, valvular heart diseases, varicose veins, vasculitis, vasculitic diffuse lung disease, venous diseases, venous thrombosis, ventricular fibrillation, vitiligo acute liver disease, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wegener's granulomatosis, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, *yersinia* and *salmonella*-associated arthropathy and the like.

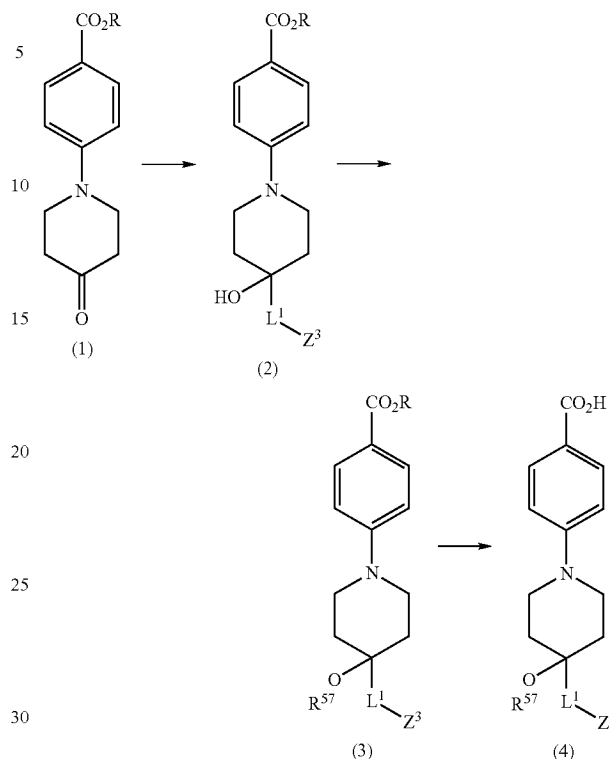
Schemes and Experimentals

The following abbreviations have the meanings indicated. ADDP means 1,1'-(azodicarbonyl)dipiperidine; AD-mix- $\beta$  means a mixture of (DHQD)<sub>2</sub>PHAL, K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, and K<sub>2</sub>SO<sub>4</sub>; 9-BBN means 9-borabicyclo(3.3.1)nonane; Boc means tert-butoxycarbonyl; (DHQD)<sub>2</sub>PHAL means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL means diisobutylaluminum hydride; DIEA means diisopropylethylamine; DMAP means N,N-dimethylaminopyridine; DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means dimethylsulfoxide; dppb means 1,4-bis(diphenylphosphino)-butane; dppe means 1,2-bis(diphenylphosphino)ethane; dppf means 1,1'-bis(diphenylphosphino)ferrocene; dppm means 1,1-bis(diphenylphosphino)methane; EDAC.HCl means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Fmoc means fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; MP-BH<sub>3</sub> means macroporous triethylammonium methylpolystyrene cyanoborohydride; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP means N-methylpyrrolidine; PPh<sub>3</sub> means triphenylphosphine.

The following schemes are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. Compounds of this invention may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

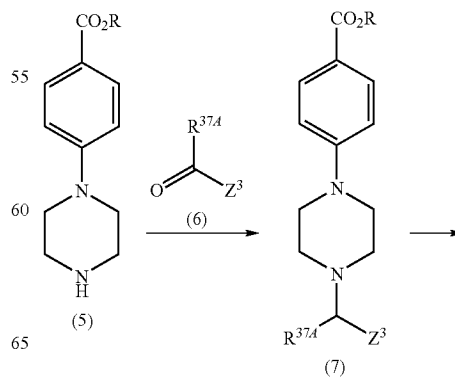
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SCHEME 1



Compounds of Formula (4) can be prepared as shown in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (1), which are representative of the compounds of the present invention. Compounds of Formula (1) wherein R is alkyl, can be converted to compounds of Formula (2) using Z<sup>3</sup>L<sup>1</sup>MgX<sup>1</sup>, wherein X<sup>1</sup> is a halide, in a solvent such as but not limited to ether or tetrahydrofuran. Compounds of Formula (3) can be prepared from compounds of Formula (2) using a strong base such as NaH and R<sup>57</sup>X<sup>2</sup>, wherein X<sup>2</sup> is a halide and R<sup>57</sup> is as described herein. Compounds of Formula (3), when treated with aqueous NaOH or LiOH, will provide compounds of Formula (4).

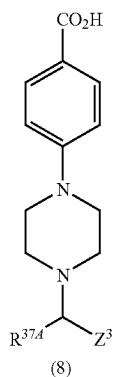
SCHEME 2



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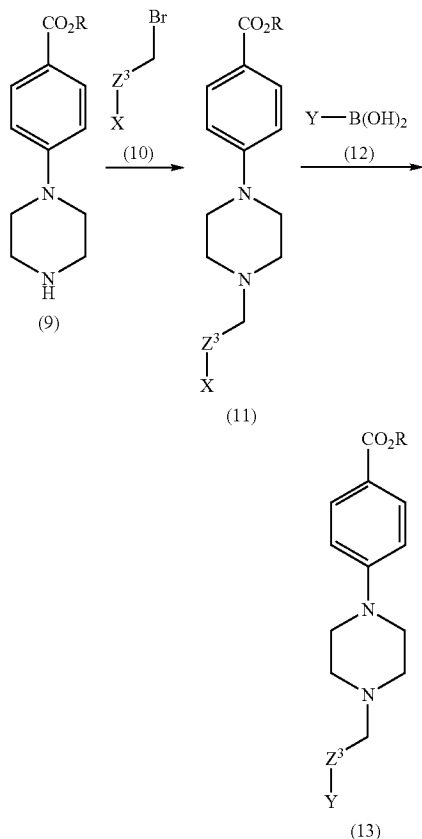
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As shown in SCHEME 2, compounds of Formula (5) can be reacted with compounds of Formula (6) and a reducing agent to provide compounds of Formula (7). Examples of reducing agents include sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, polymer supported cyanoborohydride, and the like. The reaction is typically performed in a solvent such as but not limited to methanol, tetrahydrofuran, and dichloromethane or mixtures thereof. Compounds of Formula (8) can be prepared from compounds of Formula (7) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

SCHEME 3

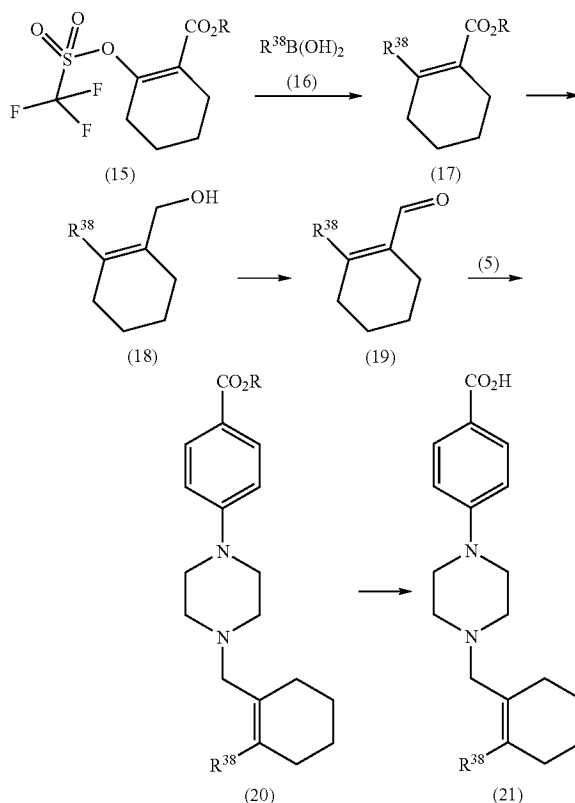


Compounds of Formula (9), when reacted with a compound of Formula (10) wherein X is a halide or triflate, and a

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base will provide a compound of Formula (11). Bases useful in the reaction include triethylamine, diisopropylethylamine and the like. Compounds of Formula (13), wherein Y is as described herein for substituents on  $Z^3$ , can be prepared from compounds of Formula (11) and compounds of Formula (12) using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (14) can be prepared from compounds of Formula (13) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

SCHEME 4



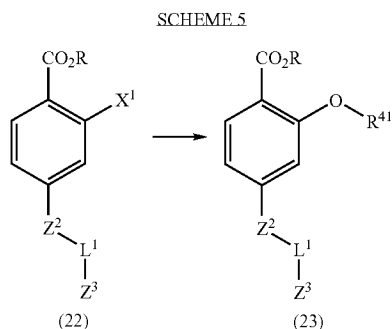
As shown in SCHEME 4, compounds of Formula (17) can be prepared from compounds of Formula (15) and compounds of Formula (16), wherein R is alkyl and  $R^{38}$  is as described herein, using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (17) can be reduced to compounds of Formula (18) using a reducing agent such as  $LiAlH_4$  in a solvent such as but not limited to diethyl ether or THF. Compounds of Formula (19) can be prepared from compounds of Formula (18) using Dess-Martin periodinane or Swern oxidation conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (19) can be reacted with a compound of Formula (5) and a reducing agent to provide compounds of Formula (20). Examples of reducing agents include sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, polymer supported cyanoborohydride, and the like. The reaction is typically performed in a solvent such as but not limited to methanol, tetrahydrofuran, 1,2-dichloroethane, and dichloromethane or mixtures thereof. Compounds of Formula (21) can be prepared from compounds of Formula (20) as described in



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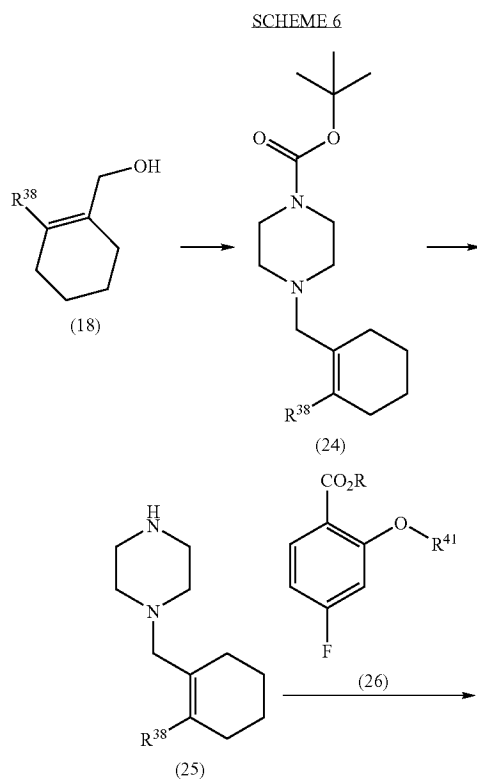
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SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).



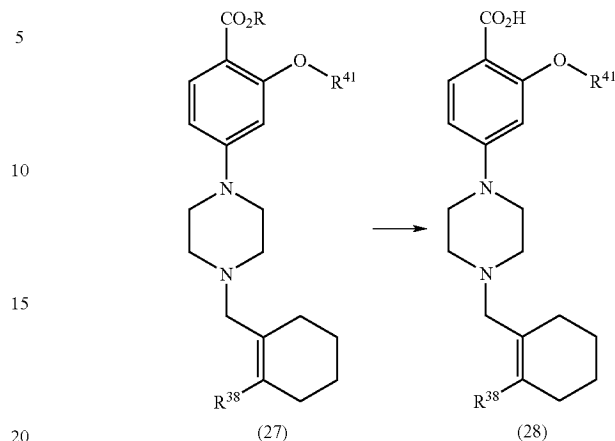
As shown in SCHEME 5, compounds of Formula (22), wherein R is alkyl, may be converted to compounds of Formula (23) by reacting the former, wherein  $X^1$  is Cl, Br, I, or  $CF_3SO_3-$ , and compounds of Formula  $R^{41}-OH$  and a catalyst, with or without a first base. Examples of catalysts include copper(I) trifluoromethanesulfonate toluene complex,  $PdCl_2$ ,  $Pd(OAc)_2$ , and  $Pd_2(dba)_3$ . Examples of first bases include triethylamine, N,N-diisopropylethylamine,  $Cs_2CO_3$ ,  $Na_2CO_3$ ,  $K_3PO_4$ , and mixtures thereof.

Compounds of Formula (22) may also be converted to compounds of Formula (23) by reacting the former, when  $X^1$  is Cl, F, or  $NO_2$ , and compounds of Formula  $R^{41}-OH$  with a first base. Examples of first bases include triethylamine, N,N-diisopropylethylamine,  $Cs_2CO_3$ ,  $Na_2CO_3$ ,  $K_3PO_4$ , and mixtures thereof.

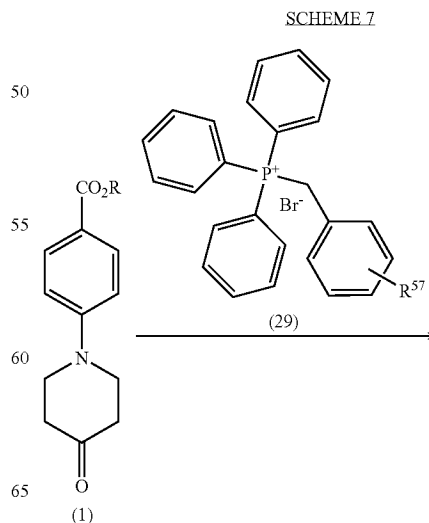


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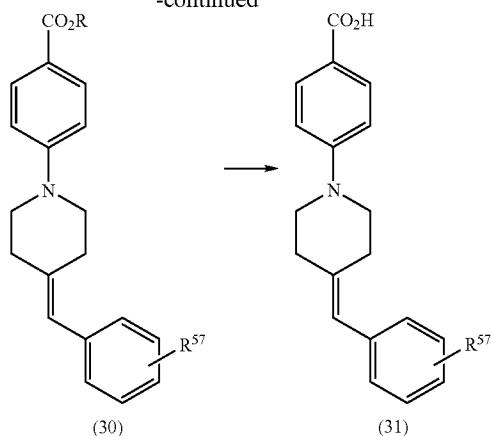
Compounds of Formula (18) can be reacted with mesyl chloride and a base such as but not limited to triethylamine, followed by N-t-butoxycarbonylpiperazine, to provide compounds of Formula (24). Compounds of Formula (25) can be prepared by reacting compounds of Formula (24) with triethylsilane and trifluoroacetic acid. Compounds of Formula (25) can be reacted with compounds of Formula (26) and  $HK_2PO_4$  to provide compounds of Formula (27) in a solvent such as but not limited to dimethylsulfoxide. Compounds of Formula (28) can be prepared from compounds of Formula (27) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).



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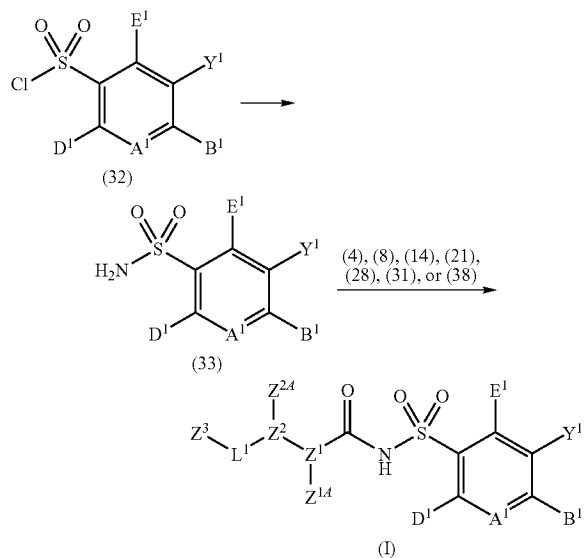
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As shown in SCHEME 7, compounds of Formula (1) can be reacted with an appropriate triphenylphosphonium bromide of Formula (29) and a base such as but not limited to sodium hydride or n-butyllithium to provide compounds of Formula (30). The reaction is typically performed in a solvent such as THF or DMSO. Compounds of Formula (31) can be prepared from compounds of Formula (30) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

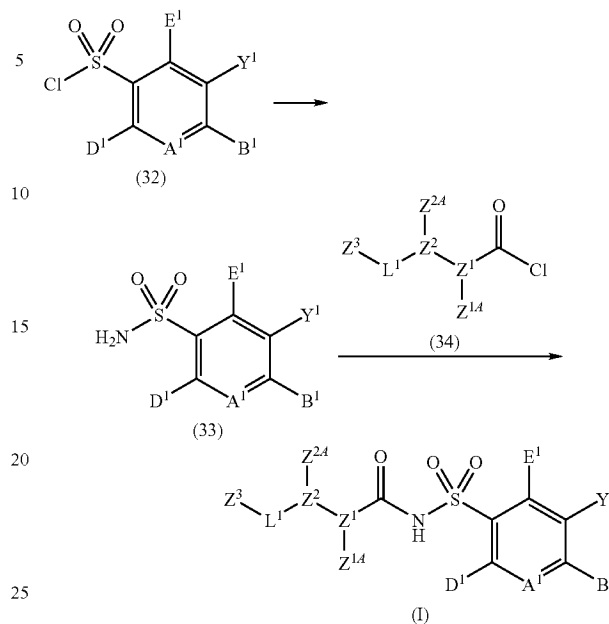
SCHEME 8



As shown in SCHEME 8, compounds of Formula (32), which can be prepared as described herein, may be converted to compounds of Formula (33) by reacting the former with ammonia. Compounds of Formula (33) may be converted to compounds of Formula (I) by reacting the former and compounds of Formula (4), (8), (14), (21), (28), (31), or (38) and a coupling agent, with or without a first base. Examples of coupling agents include 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride, 1,1'-carbonyldiimidazole, and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate. Examples of first bases include triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, and mixtures thereof.

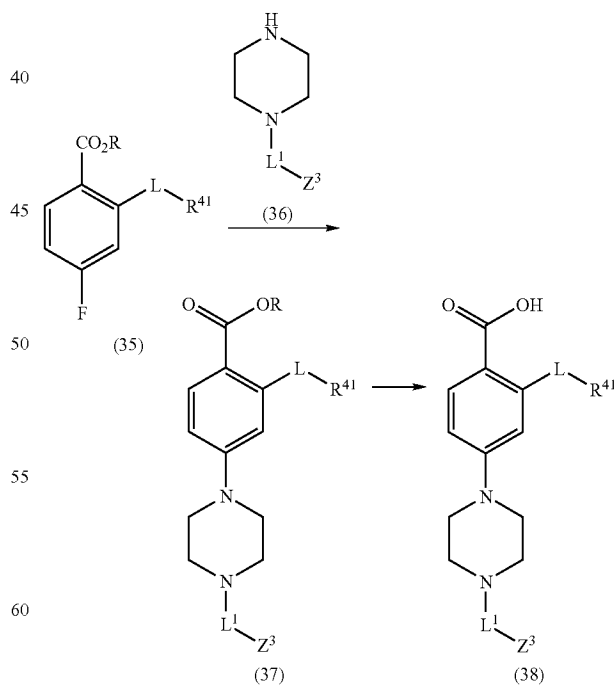
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SCHEME 9



Compounds of Formula (33), prepared as described in SCHEME 8, may also be converted to compounds of Formula (I) by reacting the former and compounds of Formula (34) and a first base. Examples of first bases include but are not limited to sodium hydride, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, and mixtures thereof.

SCHEME 10



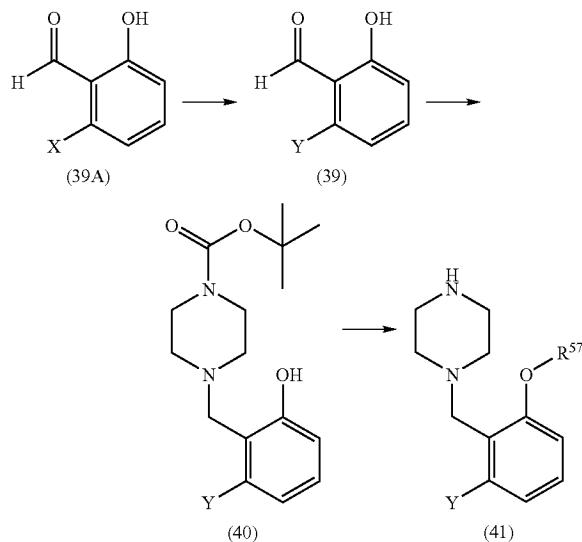
As shown in SCHEME 10, compounds of Formula (35), wherein L is a bond, alkyl, O, S, S(O), S(O)<sub>2</sub>, NH, etc., can be reacted with compounds of Formula (36), to provide com-

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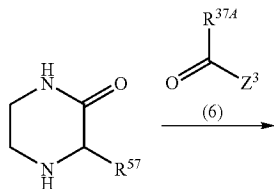
pounds of Formula (37). The reaction is typically performed at elevated temperatures in a solvent such as but not limited to dimethylsulfoxide, and may require the use of a base such as but not limited to potassium phosphate, potassium carbonate, and the like. Compounds of Formula (38) can be prepared from compounds of Formula (37) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

SCHEME 11

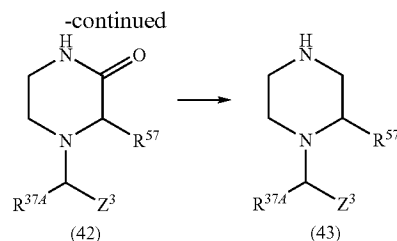


Compounds of Formula (39), wherein Y is as described herein for substituents on  $Z^3$ , can be prepared from compounds of Formula (39A) wherein X is a halide or triflate, and  $Y=B(OH)_2$  using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (39) can be reacted with tert-butyl piperazine-1-carboxylate and a reducing agent such as sodium triacetoxyborohydride to provide compounds of Formula (40). The reaction is typically performed in a solvent such as but not limited to methylene chloride. Compounds of Formula (41) can be prepared from compounds of Formula (40) by reacting the latter with  $R^{57}X$ , wherein X is a halide, and NaH in a solvent such as N,N-dimethylformamide, and then the resulting material can be treated with triethylsilane and trifluoroacetic acid in dichloromethane. Compounds of Formula (41) can be used as described in Scheme 10 wherein  $L^1-Z^3$  is as shown in Formula (41).

SCHEME 12



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As shown in SCHEME 12, substituted piperazin-2-ones wherein  $R^{57}$  is alkyl, can be reacted with compounds of Formula (6) and a reducing agent such as sodium triacetoxyborohydride in dichloromethane to provide compounds of Formula (42). Compounds of Formula (42) can be reduced to compounds of Formula (43) using a reducing agent such as but not limited to lithium aluminum hydride in a solvent such as but not limited to tetrahydrofuran. Compounds of Formula (43) can be used as described in Scheme 10 wherein  $L^1-Z^3$  is as shown in Formula (43).

The following examples are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. The exemplified compounds were named using ACD/ChemSketch Version 5.06 (5 Jun. 2001, Advanced Chemistry Development Inc., Toronto, Ontario), ACD/ChemSketch Version 12.01 (13 May 2009), Advanced Chemistry Development Inc., Toronto, Ontario), or ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, Mass.). Intermediates were named using ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, Mass.).

## Example 1

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 1A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)piperazine-1-carboxylate

4'-Chlorobiphenyl-2-carboxaldehyde (4.1 g), tert-butyl piperazine-1-carboxylate (4.23 g), and sodium triacetoxyborohydride (5.61 g) in  $CH_2Cl_2$  (60 mL) were stirred for 24 hours. The reaction was quenched with methanol and poured into ether. The solution was washed with water and brine, concentrated, and chromatographed on silica gel with 2-25% ethyl acetate/hexanes.

## Example 1B

1-((4'-chlorobiphenyl-2-yl)methyl)piperazine

EXAMPLE 1A (3.0 g) and triethylsilane (1 mL) were stirred in  $CH_2Cl_2$  (30 mL) and trifluoroacetic acid (30 mL) for 2 hours, and the reaction was concentrated, and then taken up in ether and concentrated again. The material was taken up in dichloromethane (200 mL) and  $NaHCO_3$  solution (100 mL), and partitioned. The organic layer was dried over  $Na_2SO_4$ , and condensed to give the title compound.

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## Example 1C

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-fluorobenzoate

Tert-butyl 4-bromo-2-fluorobenzoate (14.0 g), EXAMPLE 1B (16.05 g), Pd<sub>2</sub>(dba)<sub>3</sub> (tris(dibenzylideneacetone)dipalladium(0)) (1.40 g), 2-(di-tert-butylphosphino)biphenyl (1.82 g), and K<sub>3</sub>PO<sub>4</sub> (16.2 g) were stirred in 1,2-dimethoxyethane (300 mL) at 80° C. for 24 hours. The reaction was cooled and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 1D

tert-butyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

1H-Pyrrolo[2,3-B]pyridine-5-ol (167 mg), EXAMPLE 1C (500 mg), and Cs<sub>2</sub>CO<sub>3</sub> (508 mg) were stirred in dimethylsulfoxide (5 mL) at 130° C. for 24 hours. The mixture was cooled, diluted with ethyl acetate, washed three times with water, and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The crude product was chromatographed on silica gel with 25% ethyl acetate/hexanes.

## Example 1E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 1D (200 mg) and triethylsilane (1 mL) were stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with NaH<sub>2</sub>PO<sub>4</sub>, and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated.

## Example 1F

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(tetrahydropyran-4-yl)methylamine (1.14 g), and triethylamine (1 g) were stirred in tetrahydrofuran (30 mL) for 24 hours. The solution was diluted with ethyl acetate, washed with NaH<sub>2</sub>PO<sub>4</sub> solution and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The product was triturated from ethyl acetate.

## Example 1G

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 1E (115 mg), EXAMPLE 1F (67 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (82 mg), and 4-dimethylaminopyridine (26 mg) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) for 24 hours. The reaction was cooled and chromatographed on silica gel with 0-5% methanol/ethyl acetate. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.48 (brs, 1H), 8.34 (br s, 1H), 8.31 (m, 1H), 7.90 (d, 1H), 7.68 (m, 1H), 7.58 (m, 2H), 7.46 (m, 4H), 7.35 (m, 2H), 7.21 (dd, 1H),

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6.76 (m, 4H), 6.28 (m, 2H), 3.02 (m, 2H), 2.89 (m, 4H), 2.80 (m, 4H), 2.40 (m, 3H), 1.59 (m, 2H), 1.25 (m, 4H), 0.87 (m, 2H).

## Example 2

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 2A

4-(3-morpholinopropylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 3-(N-morpholinyl)-propylamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 2B

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (brs, 1H), 8.60 (m, 1H), 8.43 (d, 1H), 7.94 (d, 1H), 7.64 (m, 2H), 7.54 (d, 1H), 7.45 (m, 4H), 7.33 (m, 2H), 7.23 (dd, 1H), 6.96 (d, 1H), 6.85 (m, 2H), 6.32 (d, 1H), 6.26 (d, 1H), 3.60 (m, 4H), 3.10 (m, 4H), 3.05 (m, 10H), 2.40 (m, 2H), 2.33 (m, 2H), 1.77 (m, 2H).

## Example 3

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 3A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

## Example 3B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 3A (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concen-



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trated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

## Example 3C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)  
methanol

To a mixture of LiBH<sub>4</sub> (13 g), EXAMPLE 3B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

## Example 3D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 3C (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 3E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 3D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 3F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 3G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 3F (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL). After

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2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M NaOH (69 mL) was added, followed by 30% H<sub>2</sub>O<sub>2</sub> (8.43 mL), and the solution was stirred for 1 hour. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH<sub>2</sub>PO<sub>4</sub>. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 3H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 3G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 3I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 3H (1.55 g), EXAMPLE 3E (2.42 g), and HK<sub>2</sub>PO<sub>4</sub> (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed with 3×1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 3J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 3I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 3K

tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

Tert-butyl piperidin-4-ylcarbamate (45.00 g, 225 mmol) and dihydro-2H-pyran-4(3H)-one (24.74 g, 247 mmol) were added to dichloromethane (1000 mL). Sodium triacetoxyborohydride (61.90 g, 292 mmol) was added, and the solution was stirred at room temperature for 16 hours. The solution was extracted with 1M sodium hydroxide and dried over anhydrous sodium sulfate. The solution was filtered and concentrated and purified by flash column chromatography on

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silica gel with 10% methanol (in dichloromethane) increasing to 20% methanol (in dichloromethane).

**Example 3L**

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-amine dihydrochloride

A solution of EXAMPLE 3K (52.57 g, 185 mmol) in dichloromethane (900 mL) was treated with 4M aqueous HCl (462 mL), and the solution was mixed vigorously at room temperature for 16 hours. Solvent was removed under vacuum to give crude product as the dihydrochloride salt, which was used without further purification.

**Example 3M**

3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)benzenesulfonamide

EXAMPLE 3L (22.12 g, 86 mmol) was added to 1,4-dioxane (300 mL) and water (43 mL). Triethylamine (43.6 mL, 31.6 g, 313 mmol) was added, and the mixture was stirred at room temperature until EXAMPLE 3L had completely dissolved. 4-chloro-3-nitrobenzenesulfonamide was added and the mixture was heated at 90° C. for 16 hours. The mixture was cooled, and the solvents were removed under vacuum. 10% methanol (in dichloromethane) was added and the solution was stirred vigorously at room temperature until a fine suspension was obtained. The solid was isolated by vacuum filtration and washed with dichloromethane to give pure product.

**Example 3N**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 3M for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (brs, 1H), 8.53 (br s, 1H), 8.18 (m, 1H), 8.00 (br s, 1H), 7.63 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.20 (d, 1H), 3.95 (m, 2H), 3.05 (m, 10H), 2.73 (m, 4H), 2.17 (m, 10H), 1.95 (m, 2H), 1.80 (m, 2H), 1.63 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 4**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 4A**

4-(1-methylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 4-amino-N-methylpiperidine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

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Example 4B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (brs, 1H), 8.55 (br s, 1H), 8.17 (m, 1H), 8.02 (d, 1H), 7.85 (dd, 1H), 7.51 (m, 3H), 7.35 (m, 2H), 7.18 (dd, 1H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (d, 1H), 6.20 (d, 1H), 3.90 (m, 1H), 3.09 (m, 8H), 2.77 (m, 2H), 2.05-2.30 (m, 10H), 1.95 (s, 3H), 1.39 (t, 2H), 1.24 (m, 2H), 0.93 (s, 6H).

**Example 5**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 5A**

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(tetrahydropyran-4-yl)methylamine (1.14 g), and triethylamine (1 g) in tetrahydrofuran (30 mL) were stirred overnight, neutralized with concentrated HCl and concentrated. The residue was suspended in ethyl acetate and the precipitates were collected, washed with water and dried to provide the title compound.

**Example 5B**

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

**Example 5C**

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 5B (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

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## Example 5D

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)  
methanol

To a mixture of  $\text{LiBH}_4$  (13 g), EXAMPLE 5C (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

## Example 5E

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 5D (29.3 g) and triethylamine (30 mL) in  $\text{CH}_2\text{Cl}_2$  (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 5F

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 5E (200 mg) and triethylsilane (1 mL) were stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with  $\text{NaH}_2\text{PO}_4$ , and brine, and dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated.

## Example 5G

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 5H

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 5G (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M NaOH

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(69 mL) was added, followed by 30%  $\text{H}_2\text{O}_2$  (8.43 mL), and the solution was stirred for 1 hour.  $\text{Na}_2\text{S}_2\text{O}_3$  (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid  $\text{NaH}_2\text{PO}_4$ . The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 5I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 5H (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and  $\text{K}_3\text{PO}_4$  (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 5J

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 5I (1.55 g), EXAMPLE 5F (2.42 g), and  $\text{HK}_2\text{PO}_4$  (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed with 3×1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 5K

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 5J (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to  $\text{NaH}_2\text{PO}_4$  solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 5L

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 5K (3.39 g), EXAMPLE 5A (1.87 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (2.39 g), and 4-dimethylaminopyridine (1.09 g) were stirred in  $\text{CH}_2\text{Cl}_2$  (40 mL) for 24 hours. The reaction was cooled and chromatographed on silica gel with 25-100% ethyl acetate/hexanes, then 10% methanol/ethyl acetate with 1% acetic acid, to give the product (1.62 g, 32%) as a white solid.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ ) 11.65 (br s, 1H), 8.55 (br s, 1H), 8.04 (d, 1H), 7.89 (dd, 1H), 7.51 (m, 3H), 7.33 (d, 2H), 7.08 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.84 (m, 1H), 3.30 (m, 4H), 3.07 (m, 4H),

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2.73 (m, 2H), 2.18 (m, 6H), 1.95 (m, 2H), 1.61 (dd, 2H), 1.38 (m, 2H), 1.24 (m, 4H), 0.92 (s, 6H).

## Example 6

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 6A

4-(4-methylpiperazin-1-ylamino)-3-nitrobenzenesulfonamide

A 50 mL round-bottomed flask was charged with 4-chloro-3-nitrobenzenesulfonamide (1 g, 4.23 mmol), 4-methylpiperazin-1-amine dihydrochloride (1 g, 5.32 mmol), and N<sup>1</sup>,N<sup>1</sup>,N<sup>2</sup>,N<sup>2</sup>-tetramethylethane-1,2-diamine (3 mL, 20.01 mmol) in dioxane (10 mL). The reaction mixture was refluxed for 12 hours. After this time, the reaction mixture was cooled to room temperature, the salt filtered off via a Buchner funnel, and the solvent removed in vacuo. The crude product was added to a silica gel column (Analogix, SF65-200 g) and purified by eluting with 0-5% methanol in dichloromethane.

## Example 6B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 6A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (brs, 1H), 9.09 (br s, 1H), 8.47 (d, 1H), 8.24 (dd, 1H), 7.99 (d, 1H), 7.50 (m, 4H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.35 (d, 1H), 6.20 (d, 1H), 3.04 (m, 4H), 2.89 (m, 4H), 2.73 (m, 2H), 2.34 (s, 3H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.38 (t, 2H), 1.05 (m, 4H), 0.93 (s, 6H).

## Example 7

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

## Example 7A

ethyl 2-(9H-carbazol-4-yloxy)-4-fluorobenzoate

This EXAMPLE was prepared by substituting ethyl 2,4-difluorobenzoate for methyl 2,4-difluorobenzoate and 4-hydroxycarbazole for EXAMPLE 3G in EXAMPLE 3H.

## Example 7B

ethyl 2-(9H-carbazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate

This EXAMPLE was prepared by substituting EXAMPLE 7A for EXAMPLE 3H in EXAMPLE 3I.

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## Example 7C

2-(9H-carbazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

This EXAMPLE was prepared by substituting EXAMPLE 7B for EXAMPLE 3I in EXAMPLE 3J, except here upon completion of the reaction, water and 2N HCl were added to adjust the pH to 2, and the HCl salt of the product was extracted using CHCl<sub>3</sub>/CH<sub>3</sub>OH.

## Example 7D

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 7C for EXAMPLE 1E and EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G, except here the purification was done by preparative HPLC using a C18 column, 250×50 mm, 10μ, and eluting with a gradient of 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a bistrifluoroacetate salt. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.82 (brs, 1H), 11.40 (s, 1H), 9.70, 9.40 (both v brs, total 2H), 8.40 (d, 1H), 8.10 (br d, 1H), 7.90 (br d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.48 (d, 1H), 7.38 (m, 3H), 7.22 (m, 2H), 7.07 (m, 4H), 6.78 (dd, 1H), 6.43 (dd, 1H), 6.19 (s, 1H), 3.97 (m, 1H), 3.80 (m, 2H), 3.60, 3.30, 3.10, 2.80 (all br m, total 11H), 2.20, 2.10, 2.00 (all br m, total 8H), 1.78 (m, 2H), 1.42 (m, 2H), 1.25 (m, 2H), 0.92 (s, 6H).

## Example 8

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

## Example 8A

3-nitro-4-(3-(pyrrolidin-1-yl)propylamino)benzenesulfonamide

This EXAMPLE was prepared by substituting 3-(pyrrolidin-1-yl)propan-1-amine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 8B

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 7C for EXAMPLE 1E and EXAMPLE 8A for EXAMPLE 1F in EXAMPLE 1G, except here the purification was done by preparative HPLC using a C18 column, 250×50 mm, 10μ, and eluting with a gradient of 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a bistrifluoroacetate salt. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.80 (brs, 1H), 11.42 (s, 1H), 9.50, 9.25 (both v brs, total 2H), 8.58 (br t, 1H), 8.43 (d, 1H), 7.91 (d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.38 (m, 3H), 7.23 (m, 2H), 7.07 (m, 3H),



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6.93 (d, 1H), 6.78 (dd, 1H), 6.44 (dd, 1H), 6.18 (s, 1H), 3.70, 3.60, 3.20, 3.00 (all br m, total 18H), 2.18 (br m, 2H), 2.00-1.80 (envelope, 8H), 1.42 (m, 2H), 0.92 (s, 6H).

Example 9

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{(4-morpholin-4-ylcyclohexyl)amino}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 9A

Trans-tert-butyl 4-morpholinocyclohexylcarbamate

A solution of tert-butyl-4-aminocyclohexylcarbamate (20.32 g, 95 mmol), bis(2-bromoethyl)ether (14.30 ml, 114 mmol) and triethylamine (33.0 ml, 237 mmol) in N,N-dimethylformamide (200 ml) was stirred for 16 hours at 70° C. The reaction mixture was cooled down to room temperature, concentrated and the product was extracted with ethyl acetate. The organic layer was washed with sodium carbonate solution (15% aq.), dried and concentrated. The product was used in next step without purification.

Example 9B

Trans-4-morpholinocyclohexanamine dihydrochloride

To a solution of trans-tert-butyl-4-morpholinocyclohexylcarbamate (19.2 g, 67.5 mmol) in dichloromethane (100 ml) was added HCl (100 ml, 400 mmol) (4M in dioxane) and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was diluted with ether and solid salt was filtered off, and dried in an oven.

Example 9C

Trans-4-(4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

A solution of trans-4-morpholinocyclohexanamine dihydrochloride (5 g, 19.44 mmol), 4-fluoro-3-nitrobenzenesulfonamide (4.32 g, 19.63 mmol) and triethylamine (20 ml, 143 mmol) in tetrahydrofuran (60 ml) was stirred for 16 hours at room temperature. The solid product was filtered off, washed with tetrahydrofuran, ether, dichloromethane (3×) and dried under vacuum.

Example 9D

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{(4-morpholin-4-ylcyclohexyl)amino}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 9C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (brs, 1H), 8.49 (br s, 1H), 8.12 (m, 1H), 7.99 (br s, 1H), 7.71 (m, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 7.01 (m, 1H), 6.65 (dd, 1H), 6.36 (d, 1H), 6.21 (d, 1H), 3.60 (m, 4H), 3.04 (m, 4H), 2.73 (m, 2H), 2.57 (m, 2H), 2.42 (m,

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1H), 2.18 (m, 6H), 2.05 (m, 2H), 1.95 (m, 2H), 1.90 (m, 2H), 1.38 (m, 6H), 1.15 (m, 3H), 0.92 (s, 6H).

Example 10

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{(2-methoxyethyl)amino}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 10A

4-(2-methoxyethylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 2-methoxyethylamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

Example 10B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{(2-methoxyethyl)amino}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 10A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (brs, 1H), 8.58-8.49 (m, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.79 (m, 1H), 7.49 (m, 3H), 7.34 (m, 2H), 7.06 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.61-3.51 (m, 4H), 3.31 (s, 3H), 3.07 (m, 4H), 2.74 (m, 2H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Example 11

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 11A

(S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide and (R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

This EXAMPLE was prepared by substituting (tetrahydro-2H-pyran-3-yl)methanamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

Example 11B

(S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

The racemic mixture of EXAMPLE 11A was resolved by chiral SFC on an AD column (21 mm i.d. x 250 mm in length) using a gradient of 10-30% 0.1% diethylamine methanol in

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CO<sub>2</sub> over 15 minutes (oven temperature: 40° C.; flow rate: 40 mL/minute) to provide the title compound.

## Example 11C

(R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

The racemic mixture of EXAMPLE 11A was resolved by chiral SFC on an AD column (21 mm i.d.x 250 mm in length) using a gradient of 10-30% 0.1% diethylamine methanol in CO<sub>2</sub> over 15 minutes (oven temperature: 40° C.; flow rate: 40 mL/minute) to provide the title compound.

## Example 11D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a mixture of EXAMPLE 3J (59.8 mg, 0.105 mmol), EXAMPLE 11B (33 mg, 0.105 mmol) and N,N-dimethylpyridin-4-amine (38.4 mg, 0.314 mmol) in dichloromethane (5 ml) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (24.07 mg, 0.13 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.40 (s, br, 1H), 8.53-8.58 (m, 2H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47-7.54 (m, 3H), 7.34 (d, 2H), 7.02-7.09 (m, 3H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.79 (dd, 1H), 3.69-3.73 (m, 1H), 3.22-3.37 (m, 3H), 3.16-3.21 (m, 1H), 3.07 (s, 4H), 2.74 (s, 2H), 2.09-2.24 (m, 6H), 1.95 (s, 2H), 1.86-1.93 (m, 1H), 1.79-1.85 (m, 1H), 1.58-1.64 (m, 1H), 1.42-1.51 (m, 1H), 1.38 (t, 2H), 1.25-1.34 (m, 1H), 0.92 (s, 6H).

## Example 12

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 12A

4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

(1,4-Dioxan-2-yl)methanol (380 mg, 3.22 mmol) in tetrahydrofuran (30 ml) was treated with sodium hydride (60%) (245 mg, 6.13 mmol) at room temperature for 30 minutes. The reaction mixture was cooled in an ice bath and 4-fluoro-3-nitrobenzenesulfonamide (675 mg, 3.06 mmol) was added. The resulting mixture was stirred at room temperature for 2 hours and another portion of sodium hydride (60%) (245 mg, 6.13 mmol) was added. The reaction mixture was stirred overnight and quenched with ice water (3 ml). The cloudy

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mixture was filtered and the filtrate was concentrated. The residue was triturated with methanol to give the title compound.

## Example 12B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 12A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.42 (s, br, 1H), 8.34 (s, 1H), 8.03 (d, 2H), 7.48-7.55 (m, 3H), 7.41 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.20-4.28 (m, 2H), 3.85-3.91 (m, 1H), 3.82 (dd, 1H), 3.74-3.78 (m, 1H), 3.59-3.69 (m, 2H), 3.41-3.51 (m, 2H), 3.05-3.17 (m, 4H), 2.83 (s, br, 2H), 2.27 (s, br, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 13

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 11C in place of EXAMPLE 11B. The proton NMR spectra of EXAMPLE 13 and EXAMPLE 11D are identical. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.40 (s, br, 1H), 8.53-8.58 (m, 2H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47-7.54 (m, 3H), 7.34 (d, 2H), 7.02-7.09 (m, 3H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.79 (dd, 1H), 3.69-3.73 (m, 1H), 3.22-3.37 (m, 3H), 3.16-3.21 (m, 1H), 3.07 (s, 4H), 2.74 (s, 2H), 2.09-2.24 (m, 6H), 1.95 (s, 2H), 1.86-1.93 (m, 1H), 1.79-1.85 (m, 1H), 1.58-1.64 (m, 1H), 1.42-1.51 (m, 1H), 1.38 (t, 2H), 1.25-1.34 (m, 1H), 0.92 (s, 6H).

## Example 14

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using naphthalene-2-sulfonamide (47 mg, 0.227 mmol) in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.82 (s, 1H), 11.69 (s, 1H), 8.51 (s, 1H), 8.08 (d, 1H), 8.05 (d, 1H), 7.97 (dd, 2H), 7.82 (dd, 1H), 7.66-7.71 (m, 1H), 7.63 (t, 1H), 7.54 (d, 1H), 7.47-7.52 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.65 (dd, 1H), 6.39 (dd, 1H), 6.18 (s, 1H), 3.04 (s, 4H), 2.72 (s, 2H), 2.10-2.20 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

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## Example 15

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 15A

methyl 6,6-dimethyl-4-oxotetrahydro-2H-pyran-3-carboxylate

To a suspension of hexane-washed NaH (0.72 g, 60% in mineral oil) in tetrahydrofuran (30 mL) was added a solution of 2,2-dimethyldihydro-2H-pyran-4(3H)-one (2.0 g) in tetrahydrofuran (20 mL). The suspension was stirred at room temperature for 30 minutes. The dimethylcarbonate (6.31 mL) was added dropwise by syringe. The mixture was heated to reflux for 4 h. LC/MS showed the expected product as the major product. The mixture was acidified with 5% HCl and extracted with dichloromethane (100 mL×3) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation, the crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

## Example 15B

methyl 6,6-dimethyl-4-(trifluoromethylsulfonyloxy)-5,6-dihydro-2H-pyran-3-carboxylate

To a cooled (0° C.) stirring suspension of NaH (0.983 g, 60% in mineral oil) in ether (50 mL) was added EXAMPLE 15A (3.2 g). The mixture was stirred at 0° C. for 30 minutes before the addition of Tf<sub>2</sub>O (4.2 mL). The mixture was then stirred at room temperature overnight. The mixture was diluted with ether (200 mL) and washed with 5% HCl, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, evaporation of solvent gave the crude product which was used in the next step without further purification.

## Example 15C

methyl 4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carboxylate

To a solution of EXAMPLE 15B (2.88 g), 4-chlorophenylboronic acid (1.88 g) and Pd(Ph<sub>3</sub>P)<sub>4</sub> (0.578 g) in toluene (40 mL) and ethanol (10 mL) was added 2N Na<sub>2</sub>CO<sub>3</sub> (10 mL). The mixture was stirred at reflux overnight. The mixture was diluted ether (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent, the residue was loaded on a column and eluted with 3% ethyl acetate in hexane to give the product.

## Example 15D

(4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methanol

To a solution of EXAMPLE 15C (1.6 g) in ether (20 mL) was added LiAlH<sub>4</sub> (1.2 g). The mixture was stirred for 4 hours. The mixture was acidified carefully with 5% HCl and extracted with ethyl acetate (100 mL×3) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After concentration, the

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crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

## Example 15E

4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carbaldehyde

To a solution of oxalyl chloride (1.1 g) in dichloromethane (30 mL) at -78° C. was added dimethylsulfoxide (6.12 mL). The mixture was stirred at the temperature for 30 minutes, and then a solution of EXAMPLE 15D (1.2 g) in dichloromethane (10 mL) was added. The mixture was stirred at -78° C. for 2 hours before the addition of triethylamine (10 mL). The mixture was stirred overnight and the temperature was allowed to rise to room temperature. The mixture was diluted with ether (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration of the solvent and column purification (5% ethyl acetate in hexane) gave the product.

## Example 15F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(piperazin-1-yl)benzoate

A mixture of EXAMPLE 3H (20.5 g) and piperazine (37.0 g) in dimethylsulfoxide (200 mL) was heated to 110° C. for 24 hours, and the mixture was allowed to cool to room temperature. The mixture was poured into water (1 L), extracted three times with dichloromethane, and the combined extracts were washed with 2× water, and brine and filtered and concentrated to give the pure product.

## Example 15G

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 15E (100 mg) and EXAMPLE 15F (177 mg) in dichloromethane (10 mL) was added sodium triacetoxyborohydride (154 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2% NaOH, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum. The residue was loaded on a column and eluted with 30% ethyl acetate in hexane to give the pure product.

## Example 15H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoic acid

To a solution of EXAMPLE 15G (254 mg) in tetrahydrofuran (4 mL), methanol (2 mL) and water (2 mL) was added LiOH H<sub>2</sub>O (126 mg). The mixture was stirred overnight. The mixture was then neutralized with 5% HCl and diluted with ethyl acetate (200 mL). After washing with brine, it was dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of solvent gave the product.

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## Example 15I

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-  
2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-  
4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]  
phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-  
yloxy)benzamide

The title compound was prepared as described in  
EXAMPLE 1G, substituting EXAMPLE 1E with  
EXAMPLE 15H. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>)  
δ 11.68 (br s, 1H), 11.42 (s, 1H), 8.60 (m, 1H), 8.57 (d, 1H),  
8.05 (d, 1H), 7.80 (dd, 1H), 7.48-7.54 (m, 3H), 7.38 (d, 2H),  
7.12 (m, 3H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.11  
(s, 2H), 3.85 (m, 2H), 3.27 (m, 6H), 3.07 (m, 2H), 2.84 (m,  
2H), 2.14 (m, 5H), 1.92 (m, 1H), 1.42 (m, 2H), 1.24 (m, 2H),  
1.10 (s, 6H).

## Example 16

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxy-  
ethyl)amino]-3-[(trifluoromethyl)sulfonyl]  
phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-  
yloxy)benzamide

## Example 16A

4-(2-methoxyethylamino)-3-(trifluoromethylsulfo-  
nyl)benzenesulfonamide

4-Fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide  
(1.536 g, 5 mmol), 2-methoxyethanamine (0.376 g, 5 mmol),  
and triethylamine (1.939 g, 15 mmol) in anhydrous tetrahy-  
drofuran (30 mL) solution was heated at 55° C. for 3 hours.  
The solution was diluted with ethyl acetate, washed with  
water and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the filtrate  
was concentrated. The crude material was used in the next  
step without further purification.

## Example 16B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxy-  
ethyl)amino]-3-[(trifluoromethyl)sulfonyl]  
phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-  
yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE  
3J for EXAMPLE 1E and EXAMPLE 16A for EXAMPLE  
1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfox-  
ide-d<sub>6</sub>) δ 11.67 (brs, 1H), 8.14 (m, 1H), 8.03 (d, 1H), 7.91 (d,  
1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.19 (s, 1H), 7.04 (m, 3H),  
6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.51 (m, 4H), 3.28  
(s, 3H), 3.06 (m, 4H), 2.75 (m, 2H), 2.17 (m, 6H), 1.95 (m,  
2H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 17

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]  
pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-  
ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]  
phenyl}sulfonyl)benzamide

## Example 17A

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trif-  
luoromethylsulfonyl)benzenesulfonamide

This EXAMPLE was prepared by substituting 1-(tetrahy-  
dropyran-4-yl)methylamine for 2-methoxyethanamine in  
EXAMPLE 16A.

## Example 17B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]  
pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-  
ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]  
phenyl}sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE  
3J for EXAMPLE 1E and EXAMPLE 17A for EXAMPLE  
1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfox-  
ide-d<sub>6</sub>) δ 11.70 (brs, 1H), 8.15 (m, 1H), 8.04 (d, 1H), 7.92 (d,  
1H), 7.51 (m, 3H), 7.34 (d, 2H), 7.19 (s, 1H), 7.05 (m, 3H),  
6.68 (dd, 1H), 6.40 (m, 1H), 6.18 (d, 1H), 3.85 (m, 2H), 3.25  
(m, 4H), 3.07 (m, 4H), 2.77 (m, 2H), 2.17 (m, 6H), 1.95 (m,  
2H), 1.84 (m, 1H), 1.54 (m, 2H), 1.39 (t, 2H), 1.24 (m, 2H),  
0.93 (s, 6H).

## Example 18

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-  
yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylm-  
ethyl)amino]phenyl}sulfonyl)benzamide

## Example 18A

methyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

A mixture of 5-hydroxyindole (8.5 g), methyl 2,4-difluo-  
robenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL)  
at 115° C. was stirred for 24 hours. The reaction was cooled,  
diluted with ether (600 mL), and washed twice with water,  
and brine, and concentrated. The crude product was chro-  
matographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 18B

methyl 2-(1H-indol-5-yloxy)-4-((2-(4-chlorophe-  
nyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-  
1-yl)benzoate

A mixture of EXAMPLE 18A (1.7 g), EXAMPLE 3E (1.8  
g), and HK<sub>2</sub>PO<sub>4</sub> (1.21 g) in dimethylsulfoxide (20 mL) at  
135° C. was stirred for 24 hours. The reaction was cooled,  
diluted with ether (400 mL), and washed with 3×1M NaOH,  
and brine, and concentrated. The crude product was chro-  
matographed on silica gel with 10-50% ethyl acetate/hex-  
anes.



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## Example 18C

2-(1H-indol-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 18B (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 18D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 3J with EXAMPLE 18C, and EXAMPLE 1F for EXAMPLE 11B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.18 (s, 2H), 8.59-8.64 (m, 2H), 7.80 (dd, 1H), 7.52 (d, 1H), 7.39-7.42 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.10 (d, 1H), 7.03 (d, 2H), 6.8 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.14 (d, 1H), 3.85 (dd, 2H), 3.24-3.32 (m, 4H), 3.03 (s, 3H), 2.73 (s, 2H), 2.12-2.17 (m, 5H), 1.68-1.94 (m, 3H), 1.61 (d, 2H), 1.37 (t, 2H), 1.24-1.27 (m, 2H), 0.92 (s, 6H).

## Example 19

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 11B with EXAMPLE 9B and EXAMPLE 3J with EXAMPLE 18C. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.29 (s, 1H), 9.29 (d, J=2.1 Hz, 1H), 8.37 (d, J=7.6 Hz, 1H), 8.32 (dd, J=9.3, 2.3 Hz, 1H), 8.18 (d, J=8.8 Hz, 1H), 7.52-7.57 (m, 2H), 7.39-7.47 (m, 3H), 7.10 (dd, J=8.7, 2.3 Hz, 1H), 7.05-7.08 (m, 2H), 6.90 (d, J=9.5 Hz, 1H), 6.74 (dd, J=9.0, 2.3 Hz, 1H), 6.59-6.63 (m, 1H), 6.55 (d, J=2.4 Hz, 1H), 3.72-3.78 (m, 4H), 3.33-3.43 (m, 1H), 2.99-3.09 (m, 4H), 2.76 (s, 2H), 2.46-2.54 (m, 4H), 2.16-2.29 (m, 3H), 2.09-2.14 (m, 4H), 2.05 (d, J=11.9 Hz, 2H), 1.97 (d, J=1.8 Hz, 2H), 1.87 (d, J=11.6 Hz, 2H), 1.19-1.42 (m, 6H), 0.93 (s, 6H).

## Example 20

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 11B with EXAMPLE 10A and EXAMPLE 3J with EXAMPLE 18C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.20 (br. s, 1H), 11.15 (s, 1H), 8.59 (m, 2H), 7.81 (dd, 1H), 7.50 (d, 1H), 7.36 (m, 4H), 7.08 (m, 4H), 6.85 (dd, 1H), 6.65 (dd, 1H), 6.38 (m, 1H), 6.14 (m, 1H), 3.58 (m, 4H), 3.30 (s, 3H), 3.03 (m, 4H), 2.73 (s, 2H), 2.15 (m, 6H), 1.96 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

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## Example 21

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-([3-nitro-4-((3S)-tetrahydro-2H-pyran-3-ylmethyl)amino]phenyl)sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 3J with EXAMPLE 18C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.17 (s, 2H), 8.53-8.65 (m, 2H), 7.80 (d, 1H), 7.51 (d, 1H), 7.38-7.44 (m, 2H), 7.33 (d, 2H), 7.15 (s, 1H), 7.02-7.09 (m, 3H), 6.82-6.92 (m, 1H), 6.65 (d, 1H), 6.39 (s, 1H), 6.14 (s, 1H), 3.68-3.82 (m, 2H), 3.22-3.32 (m, 2H), 3.13-3.22 (m, 1H), 3.03 (s, 4H), 2.72 (s, 2H), 2.09-2.23 (m, 6H), 1.78-1.98 (m, 4H), 1.56-1.66 (m, 1H), 1.43-1.51 (m, 1H), 1.37 (t, 2H), 1.22-1.33 (m, 1H), 0.92 (s, 6H).

## Example 22

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-([3-nitro-4-((3R)-tetrahydro-2H-pyran-3-ylmethyl)amino]phenyl)sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 11C in place of EXAMPLE 11B, and EXAMPLE 18C in place of EXAMPLE 3J. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.17 (s, 2H), 8.53-8.65 (m, 2H), 7.80 (d, 1H), 7.51 (d, 1H), 7.38-7.44 (m, 2H), 7.33 (d, 2H), 7.15 (s, 1H), 7.02-7.09 (m, 3H), 6.82-6.92 (m, 1H), 6.65 (d, 1H), 6.39 (s, 1H), 6.14 (s, 1H), 3.68-3.82 (m, 2H), 3.22-3.32 (m, 2H), 3.13-3.22 (m, 1H), 3.03 (s, 4H), 2.72 (s, 2H), 2.09-2.23 (m, 6H), 1.78-1.98 (m, 4H), 1.56-1.66 (m, 1H), 1.43-1.51 (m, 1H), 1.37 (t, 2H), 1.22-1.33 (m, 1H), 0.92 (s, 6H).

## Example 23

4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

## Example 23A

methyl 2-(1H-indol-5-yloxy)-4-((piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 15F by replacing EXAMPLE 3H with EXAMPLE 18A.

## Example 23B

methyl 2-(1H-indol-5-yloxy)-4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 15G by replacing EXAMPLE 15F with EXAMPLE 23A.

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## Example 23C

2-(1H-indol-5-yloxy)-4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 15H by replacing EXAMPLE 15G with EXAMPLE 23B.

## Example 23D

4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino]phenyl)sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 11B with EXAMPLE 1F, and EXAMPLE 3J with EXAMPLE 23C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.20 (br s, 1H), 11.17 (s, 1H), 8.63 (t, 1H), 8.59 (d, 1H), 7.79 (dd, 1H), 7.51 (d, 1H), 7.36 (m, 3H), 7.13 (m, 2H), 6.86 (dd, 1H), 6.66 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.10 (s, 2H), 3.85 (m, 3H), 3.50 (m, 2H), 3.42 (m, 2H), 3.24 (m, 4H), 3.02 (m, 4H), 2.82 (m, 2H), 2.16 (m, 2H), 1.61 (m, 3H), 1.25 (m, 4H), 1.17 (s, 6H).

## Example 24

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 24A

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

(Tetrahydro-2H-pyran-4-yl)methanol (2.0 g) in tetrahydrofuran (20 mL) was treated with 60% NaH (1.377 g). The solution was stirred for 20 minutes at the room temperature. To this solution was added 4-fluoro-3-nitrobenzenesulfonamide (2.84 g) portion-wise. The reaction was stirred for another 2 hours. The mixture was poured into water, neutralized with 10% HCl, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20-60% ethyl acetate in hexanes.

## Example 24B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 24A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.33 (s, 1H), 8.00-8.02 (m, 2H), 7.50-7.53 (m, 3H), 7.34-7.36 (m, 3H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (d, 1H), 6.21 (s, 1H), 4.06 (d, 2H), 3.88 (dd, 2H), 3.08 (s, 4H), 2.80 (s, 2H), 2.25 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.66 (m, 2H), 1.52-1.55 (m, 1H), 1.33-1.40 (m, 4H), 0.92 (s, 6H).

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## Example 25

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((1,4-dioxan-2-ylmethyl)amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 25A

4-((1,4-dioxan-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 1F using (1,4-dioxan-2-yl)methanamine in place of (tetrahydropyran-4-yl)methanamine.

## Example 25B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((1,4-dioxan-2-ylmethyl)amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 25A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.38 (s, 1H), 8.53-8.59 (m, 2H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.46-7.54 (m, 3H), 7.34 (d, 2H), 7.09 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.75-3.86 (m, 3H), 3.58-3.68 (m, 2H), 3.45-3.52 (m, 2H), 3.35-3.43 (m, 2H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H)

## Example 26

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((2,2,2-trifluoroethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 26A

3-nitro-4-(2,2,2-trifluoroethylamino)benzenesulfonamide

The title compound was prepared by substituting 2,2,2-trifluoroethanamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 26B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((2,2,2-trifluoroethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.48 (s, 1H), 8.40 (m, 2H), 7.90 (d, 1H), 7.71 (dd, 1H), 7.59 (d, 1H), 7.40 (t, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.06 (m, 3H), 6.61 (dd, 1H), 6.26

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(m, 2H), 4.32 (m, 2H), 3.00 (m, 4H), 2.73 (s, 2H), 2.19 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 27

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 27A

3-nitro-4-(3,3,3-trifluoropropylamino)benzene-sulfonamide

The title compound was prepared by substituting 3,3,3-trifluoropropan-1-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 27B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 27A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.47 (s, 1H), 8.37 (d, 1H), 8.29 (m, 1H), 7.89 (d, 1H), 7.61 (m, 2H), 7.39 (t, 1H), 7.35 (d, 2H), 7.22 (d, 1H), 7.05 (d, 2H), 6.75 (d, 1H), 6.62 (dd, 1H), 6.27 (m, 2H), 3.59 (q, 2H), 3.00 (m, 4H), 2.73 (s, 2H), 2.66 (m, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (m, 6H).

## Example 28

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 28A

(S)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzene-sulfonamide

The racemic mixture of EXAMPLE 12A was resolved on a SFC chiral AD column to provide the title compound.

## Example 28B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 28A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 2H), 8.35 (s, 1H), 8.03 (d, 2H), 7.48-7.57 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (s, 1H), 4.19-4.30 (m, 2H), 3.85-3.92 (m, 1H), 3.73-3.85 (m, 2H), 3.58-3.70 (m, 2H), 3.40-3.52 (m, 2H), 3.10 (s, 4H), 2.85 (s, 2H), 2.18-2.39 (m, 3H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 29

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 29A

Cis-4-((4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (1.098 g) and EXAMPLE 34A (1 g) in tetrahydrofuran (20 mL) was treated with N,N-diisopropylethylamine (0.871 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography, eluted with 40-55% acetonitrile in 0.1% trifluoroacetic acid in water over 25 min to give the cis isomer EXAMPLE 29A and trans isomer EXAMPLE 34B.

## Example 29B

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 29A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.36 (s, 1H), 8.53-8.63 (m, 2H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47-7.56 (m, 3H), 7.34 (d, 2H), 7.00-7.12 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.37 (s, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.81 (dd, 2H), 1.64-1.74 (m, 1H), 1.48 (dd, 2H), 1.23-1.42 (m, 6H), 0.92 (s, 6H).

## Example 30

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 30A

(R)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

The racemic mixture of EXAMPLE 12A was resolved on a SFC chiral AD column to provide the title compound.

## Example 30B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 30A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 2H), 8.35 (s, 1H), 8.03 (d, 2H), 7.48-7.57 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39

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(dd, 1H), 6.21 (s, 1H), 4.19-4.30 (m, 2H), 3.85-3.92 (m, 1H), 3.73-3.85 (m, 2H), 3.58-3.70 (m, 2H), 3.40-3.52 (m, 2H), 3.10 (s, 4H), 2.85 (s, 2H), 2.18-2.39 (m, 3H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 31**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 25A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.46 (m, 1H), 8.54 (m, 2H), 8.45 (m, 1H), 8.03 (d, 1H), 7.83 (m, 2H), 7.50 (m, 3H), 7.34 (m, 3H), 7.12 (m, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.11 (s, 2H), 3.79 (m, 4H), 3.51 (m, 6H), 3.05 (m, 4H), 2.17 (m, 3H), 1.17 (s, 6H).

**Example 32**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 12A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.37 (d, 1H), 8.03 (m, 2H), 7.50 (m, 3H), 7.37 (d, 2H), 7.13 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.25 (m, 2H), 4.12 (s, 2H), 3.84 (m, 3H), 3.63 (m, 2H), 3.45 (m, 2H), 3.06 (m, 4H), 2.86 (m, 2H), 2.24 (m, 6H), 1.20 (m, 6H).

**Example 33**

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 9C, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.51 (d, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.76 (dd, 1H), 7.48 (m, 3H), 7.38 (d, 2H), 7.13 (d, 2H), 7.06 (d, 1H), 6.66 (dd, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 4.11 (s, 2H), 3.63 (m, 5H), 3.05 (m, 4H), 2.83 (s, 2H), 2.64 (m, 4H), 2.17 (m, 6H), 2.05 (m, 2H), 1.91 (s, 2H), 1.43 (m, 6H), 1.17 (m, 6H).

**Example 34**

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 34A**

(4-methoxycyclohexyl)methanamine  
(4-Methoxyphenyl)methanamine (1 g, 1.29 mmol) in ethanol (10 ml) was treated with 5% Rh—Al<sub>2</sub>O<sub>3</sub> (99.8 mg, 0.048

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mmol) under H<sub>2</sub> atmosphere (500 psi) at 50° C. for 16 hours. Additional 5% Rh—Al<sub>2</sub>O<sub>3</sub> (0.4 g) was added. The resulting mixture was stirred under H<sub>2</sub> atmosphere (500 psi) at 60° C. for 2 hours. The insoluble material was filtered off and the filtrate was concentrated to provide a mixture of cis and trans product as an oil, which was used in the next step without further purification.

**Example 34B**

Trans-4-((4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (1.098 g) and EXAMPLE 34A (1 g) in tetrahydrofuran (20 mL) was treated with N,N-diisopropylethylamine (0.871 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography, and was eluted with 40-55% acetonitrile in 0.1% trifluoroacetic acid in water over 25 minutes.

**Example 34C**

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 34B in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.37 (s, 1H), 8.52-8.62 (m, 2H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47-7.55 (m, 3H), 7.34 (d, 2H), 7.02-7.09 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.21-3.27 (m, 5H), 3.02-3.12 (m, 5H), 2.75 (s, 2H), 2.20 (s, 4H), 2.14 (s, 2H), 1.93-2.04 (m, 4H), 1.79 (d, 2H), 1.55-1.65 (m, 1H), 1.38 (t, 2H), 0.97-1.12 (m, 4H), 0.92 (s, 6H).

**Example 35**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 36C, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.78 (s, 1H), 8.58 (s, 1H), 8.00 (d, 1H), 7.51 (m, 3H), 7.38 (d, 2H), 7.14 (d, 2H), 6.68 (dd, 1H), 6.37 (dd, 1H), 6.23 (d, 1H), 4.31 (d, 2H), 4.13 (s, 2H), 3.88 (dd, 2H), 3.11 (m, 5H), 2.16 (m, 6H), 1.65 (m, 2H), 1.35 (m, 2H), 1.19 (s, 6H).

**Example 36**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 36A**

5-Bromo-6-chloropyridine-3-sulfonyl chloride (8.2 g) in methanol (20 mL) was cooled to 0° C. To this solution was



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added 7N NH<sub>3</sub> in methanol (80 mL). The reaction mixture was stirred overnight. The solvent was removed at low temperature, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), filtered, and concentrated. The solid was purified by flash column chromatography on silica gel using 20-100% ethyl acetate in hexanes to give the title compound.

**Example 36B**

The title compound was prepared by substituting EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

**Example 36C**

A mixture of EXAMPLE 36B (0.702 g), dicyanozinc (0.129 g), and tetrakis(triphenylphosphine)palladium(0) (0.231 g) in N,N-dimethylformamide (2 mL) was degassed via vacuum/nitrogen cycle three times. The reaction mixture was heated at 120° C. for 3 hours. After cooling, it was poured into water and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20%-60% ethyl acetate in hexanes to give the title compound.

**Example 36D**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 36C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.66 (s, 1H), 8.44 (s, 1H), 7.94 (d, 1H), 7.55 (d, 1H), 7.44 (t, 1H), 7.34-7.35 (m, 3H), 7.04 (d, 2H), 6.65 (dd, 1H), 6.32 (s, 1H), 6.24 (s, 1H), 4.26 (d, 2H), 3.86 (dd, 2H), 3.10 (s, 4H), 2.75 (s, 2H), 2.31-2.35 (m, 2H), 2.01-2.05 (m, 1H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.66 (m, 2H), 1.33-1.40 (m, 4H), 0.92 (s, 6H).

**Example 37**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 37A**

1,6-dioxaspiro[2.5]octane-2-carbonitrile

A mixture of tetrahydropyran-4-one (10 mL) and chloroacetonitrile (6.4 mL) in tert-butanol (10 mL) was stirred for 10 minutes. To this solution was added a solution of potassium tert-butoxide (12.11 g) in 200 mL of tert-butanol at room temperature over 40 minutes. The reaction mixture was stirred for 16 hours, diluted with water and quenched slowly with 1 N HCl. The solvent was partially removed by rotary evaporation. It was then extracted with ether (5×200 mL). The combined extracts were washed with brine, dried over MgSO<sub>4</sub>,

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filtered, and the filtrate was concentrated and purified by flash chromatography on silica with 3:7 to 1:1 ethyl acetate:hexanes to provide the title compound.

**Example 37B**

2-(4-fluorotetrahydro-2H-pyran-4-yl)-2-hydroxyacetonitrile

EXAMPLE 37A (11.5 g) in dichloromethane (40 mL) in a polypropylene bottle was treated with 70% hydrogen fluoride-pyridine (10.4 mL) dropwise at 0° C. The solution was allowed to warm to room temperature over 3 hours, and stirred for an additional 1.5 hours. The reaction mixture was diluted with ethyl acetate (200 mL) and poured into saturated aqueous NaHCO<sub>3</sub>. Additional solid NaHCO<sub>3</sub> was used carefully until bubbling ceased. The organic layer was isolated, and the aqueous layer was extracted with additional ethyl acetate three times (150 mL each). The combined organic layers were washed with 5% HCl (50 mL each, twice), brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give the desired product which was used directly in the next step.

**Example 37C**

(4-fluorotetrahydro-2H-pyran-4-yl)methanol

EXAMPLE 37B (11.7 g, 74 mmol) in 2-propanol (150 mL) and water (37.5 mL) was cooled to 0° C. To this solution was added NaBH<sub>4</sub> (4.20 g, 111 mmol). The solution was stirred and allowed to warm to room temperature over 3 hours. It was quenched with acetone, and stirred for another 1 hour. The clear liquid was separated from solid by decanting. Additional ethyl acetate (2×100 mL) was used to wash the solid, and the mixture was decanted. The combined organic solutions were concentrated. The residue was purified by flash chromatography, eluting with 1:1 ethyl acetate:hexanes to provide the title compound.

**Example 37D**

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

**Example 37E**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 37D in place of EXAMPLE 11B. <sup>1</sup>H NMR (dimethylsulfoxide-d<sub>6</sub>) 11.64 (s, 2H), 8.33 (s, 1H), 8.00-8.01 (m, 2H), 7.39-7.57 (m, 4H), 7.33 (d, J=8.24 Hz, 2H), 7.03 (d, J=8.54 Hz, 2H), 6.65 (dd, J=9, 1.98 Hz, 1H), 6.37-6.38 (m, 1H), 6.19 (d, J=1.53 Hz, 1H), 4.35 (d, J=20.75 Hz, 2H), 3.74-3.78 (m, 2H), 3.55-3.60 (m, 2H), 3.07 (br, 4H), 2.80 (br, 2H), 2.25 (br, 4H), 2.13 (br, 2H), 1.81-1.94 (m, 6H), 1.38 (t, J=6.26 Hz, 2H), 0.91 (s, 6H).

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## Example 38

N-{{3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 38A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting 3-cyano-4-fluorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 38B

5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)benzamide

To a solution of EXAMPLE 38A (0.455 g) in ethanol (3 mL) and tetrahydrofuran (1 mL) was added hydrogen peroxide (30% in water, 2 mL) followed by 1 N aqueous NaOH (1.024 mL) and heated to 35° C. for 3 hours. The reaction was poured into dichloromethane (50 mL) and 1N aqueous HCl (25 mL). The aqueous layer was extracted with dichloromethane (3x50 mL). The precipitate contained in the combined organic layers was collected by filtration to give the title compound.

## Example 38C

N-{{3-(amino carbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 38B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.79-11.70 (m, 1H), 11.66-11.54 (m, 1H), 9.29-9.08 (m, 1H), 8.27 (d, 1H), 8.08 (d, 1H), 7.97-7.90 (m, 1H), 7.76-7.72 (m, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.50 (d, 1H), 7.39 (d, 1H), 7.23 (d, 1H), 7.08 (d, 1H), 6.74-6.67 (m, 1H), 6.44 (s, 1H), 6.22 (s, 1H), 4.03 (d, 6H), 3.74-3.52 (m, 4H), 3.33 (s, 4H), 3.11-2.90 (m, 2H), 2.01 (s, 4H), 1.79-1.58 (m, 2H), 1.24 (s, 5H), 0.94 (s, 6H).

## Example 39

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 39A

Cis-tert-butyl-4-morpholinocyclohexylcarbamate

To a solution of morpholine (4.08 g) and tert-butyl 4-oxocyclohexylcarbamate (10 g) stirred for 24 hours at room temperature in titanium (IV) isopropoxide (27.5 mL), methanol (10 mL) was added followed by careful addition of

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sodium borohydride (3.55 g). The reaction mixture was quenched with water/NaOH solution, extracted with ether, dried over magnesium sulfate, filtered, and concentrated. The product was separated from the trans isomer and purified by flash chromatography (silica gel, 50%-100% acetone in hexanes) to provide the title compound.

## Example 39B

cis-4-morpholinocyclohexanamine bis(2,2,2-trifluoroacetate)

To a solution of EXAMPLE 39A (2.43 g) in dichloromethane (15 mL) was added trifluoroacetic acid (5 mL) and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was concentrated and the crude product was used without purification.

## Example 39C

4-(cis-4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

A solution of EXAMPLE 39B (0.40 g), 4-fluoro-3-nitrobenzenesulfonamide (0.478 g) and triethylamine (2 mL) in tetrahydrofuran (10 mL) was stirred for 3 days at room temperature. The reaction mixture was concentrated and purified by flash chromatography (silica gel, 0-30% methanol/dichloromethane) providing the product.

## Example 39D

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 39C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.30 (d, 1H), 8.64 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.67 (t, 2H), 7.44 (d, 2H), 7.06 (d, 2H), 6.91 (d, 1H), 6.74 (dd, 1H), 6.48-6.55 (m, 2H), 3.65-3.73 (m, 5H), 3.02-3.09 (m, 4H), 2.76 (s, 2H), 2.41-2.48 (m, 4H), 2.25 (t, 2H), 2.09-2.16 (m, 5H), 1.97 (s, 2H), 1.77-1.86 (m, 2H), 1.55-1.63 (m, 6H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 40

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 40A

5,6-dichloropyridine-3-sulfonamide

The title compound was prepared by substituting 5,6-dichloropyridine-3-sulfonyl chloride for 5-bromo-6-chloropyridine-3-sulfonyl chloride in EXAMPLE 36A.

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## Example 40B

5-chloro-6-((tetrahydro-2H-pyran-4-yl)methoxy)  
pyridine-3-sulfonamide

The title compound was prepared by substituting  
EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in  
EXAMPLE 24A.

## Example 40C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetra-  
hydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfo-  
nyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)  
benzamide

The title compound was prepared by substituting  
EXAMPLE 40B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H  
NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.52  
(s, 1H), 8.39 (d, 1H), 8.03 (d, 1H), 7.54 (d, 1H), 7.52 (d, 1H),  
7.50 (dd, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39  
(m, 1H), 6.21 (d, 1H), 4.25 (d, 2H), 3.87 (dd, 2H), 3.30 (m,  
2H), 3.10 (v br s, 4H), 2.90 (v br s, 2H), 2.35 (v br s, 4H), 2.17  
(br m, 2H), 2.05 (m, 1H), 1.96 (s, 2H), 1.64 (d, 2H), 1.40 (t,  
2H), 1.35 (ddd, 2H), 0.93 (s, 6H).

## Example 41

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-  
2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[5-chloro-  
6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]  
sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)  
benzamide

The title compound was prepared by substituting  
EXAMPLE 15H for EXAMPLE 3J and EXAMPLE 40B for  
EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz,  
dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.55 (d, 1H), 8.41 (d,  
1H), 8.04 (d, 1H), 7.54 (m, 2H), 7.50 (dd, 1H), 7.38 (d, 2H),  
7.14 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 4.25  
(d, 2H), 4.12 (s, 2H), 3.87 (dd, 2H), 3.30 (m, 2H), 3.10 (v br  
s, 4H), 2.90 (v br s, 2H), 2.27 (v br s, 4H), 2.17 (br m, 2H),  
2.05 (m, 1H), 1.96 (s, 2H), 1.64 (d, 2H), 1.35 (ddd, 2H), 0.97  
(s, 6H).

## Example 42

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-  
2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo  
[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-py-  
ran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]  
sulfonyl}benzamide

## Example 42A

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trif-  
luoromethyl)benzenesulfonamide

A mixture of 4-fluoro-3-(trifluoromethyl)benzenesulfona-  
mide (1.056 g), (tetrahydro-2H-pyran-4-yl)methanamine  
(0.5 g) and N,N-diisopropylethylamine (1.68 g) in anhydrous  
dimethylsulfoxide (15 mL) solution was heated at 90° C.  
overnight. The reaction mixture was cooled to room tempera-  
ture and diluted with ethyl acetate. The organic phase was

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washed with water, brine, dried over anhydrous sodium sul-  
fate, filtered and concentrated to afford the title compound.

## Example 42B

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-  
2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo  
[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-py-  
ran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]  
sulfonyl}benzamide

The title compound was prepared as described in  
EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE  
1F with EXAMPLE 15H and EXAMPLE 42A, respectively.  
<sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.73 (s, 1H),  
11.25 (s, 1H), 8.08 (d, 1H), 7.89 (d, 1H), 7.77 (m, 1H), 7.61 (d,  
1H), 7.51 (m, 2H), 7.37 (d, 2H), 7.13 (d, 2H), 6.88 (d, 1H),  
6.67 (dd, 1H), 6.53 (m, 1H), 6.43 (m, 1H), 6.15 (d, 1H), 4.11  
(s, 2H), 3.82 (dd, 2H), 3.19 (m, 5H), 3.05 (m, 4H), 2.82 (s,  
2H), 2.20 (m, 7H), 1.85 (m, 1H), 1.56 (m, 2H), 1.18 (s, 6H).

## Example 43

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-  
2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo  
[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-py-  
ran-4-ylmethyl)amino]-3-(trifluoromethyl)sulfonyl]  
phenyl}sulfonylbenzamide

The title compound was prepared as described in  
EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE  
1F with EXAMPLE 15H and EXAMPLE 17A, respectively.  
<sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H),  
11.48 (m, 1H), 8.16 (d, 1H), 8.05 (d, 1H), 7.92 (dd, 1H), 7.52  
(m, 3H), 7.37 (d, 2H), 7.27 (m, 1H), 7.11 (m, 3H), 6.68 (dd,  
1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.11 (s, 2H), 3.84 (dd, 2H),  
3.25 (m, 4H), 3.07 (m, 4H), 2.84 (m, 2H), 2.23 (m, 5H), 1.84  
(m, 1H), 1.55 (m, 2H), 1.25 (m, 3H), 1.18 (s, 6H).

## Example 44

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-  
dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-  
([4-[(4-morpholin-4-ylcyclohexyl)amino]-3-(trif-  
luoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-  
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 44A

Trans-4-(4-morpholinocyclohexylamino)-3-(trifluo-  
romethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in  
EXAMPLE 16A by replacing 2-methoxyethanamine with  
EXAMPLE 9B.

## Example 44B

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-  
dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-  
([4-[(4-morpholin-4-ylcyclohexyl)amino]-3-(trif-  
luoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-  
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in  
EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE  
1F with EXAMPLE 15H and EXAMPLE 44A, respectively.

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<sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.62 (s, 1H), 8.08 (s, 1H), 8.00 (d, 1H), 7.85 (d, 1H), 7.47 (m, 3H), 7.38 (d, 2H), 7.14 (d, 2H), 6.98 (d, 1H), 6.65 (dd, 1H), 6.55 (m, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.12 (s, 2H), 3.54 (m, 6H), 3.04 (m, 4H), 2.83 (s, 2H), 2.57 (m, 3H), 2.24 (m, 6H), 1.91 (m, 5H), 1.34 (m, 4H), 1.20 (s, 6H).

## Example 45

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 45A

4-(1-methylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 16A by replacing 2-methoxyethanamine with 1-methyl-4-aminopiperidine.

## Example 45B

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 45A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.10 (s, 1H), 7.98 (d, 1H), 7.90 (dd, 1H), 7.49 (m, 3H), 7.39 (m, 3H), 7.14 (d, 2H), 7.02 (d, 1H), 6.65 (dd, 2H), 6.36 (dd, 1H), 6.22 (d, 1H), 4.12 (s, 2H), 3.75 (m, 1H), 3.16 (m, 4H), 2.98 (m, 5H), 2.88 (m, 5H), 2.67 (s, 2H), 2.22 (m, 6H), 1.68 (m, 1H), 1.18 (s, 6H).

## Example 46

5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide

5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)nicotinamide

To EXAMPLE 36C (0.025 g) in ethanol (1 mL) and tetrahydrofuran (1 mL) was added hydrogen peroxide (30% in water, 0.5 mL) followed by 1M aqueous sodium hydroxide (0.056 mL) then another 1 mL of tetrahydrofuran. The reaction was heated to 45° C. for 2 hours, cooled, quenched with 1N

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aqueous HCl (5 mL), and the product extracted into dichloromethane (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give the title compound.

## Example 46B

5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide

The title compound was prepared by substituting EXAMPLE 46A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.31-10.09 (m, 1H), 9.09 (s, 2H), 8.93-8.81 (m, 1H), 8.28-8.18 (m, 1H), 8.03-7.87 (m, 1H), 7.77-7.68 (m, 1H), 7.59-7.51 (m, 1H), 7.48-7.41 (m, 1H), 6.91 (d, 2H), 6.59-6.48 (m, 2H), 5.97 (s, 2H), 4.50 (d, 2H), 4.08-3.98 (m, 2H), 3.45 (s, 4H), 3.13-2.99 (m, 4H), 2.82-2.68 (m, 2H), 2.19 (s, 4H), 1.86 (s, 5H), 1.61-1.35 (m, 4H), 0.94 (s, 6H).

## Example 47

N-({5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 47A

5-bromo-6-((1-methylpiperidin-4-yl)methoxy)pyridine-3-sulfonamide

To (1-methylpiperidin-4-yl)methanol (0.109 g) in tetrahydrofuran (2 mL) was added sodium hydride (0.136 g). After 30 minutes, EXAMPLE 36A (0.230 g) was added as a solution in tetrahydrofuran (1 mL) and the reaction was heated to 50° C. After 4 hours, the reaction was cooled, poured into water (10 mL) and dichloromethane (50 mL), and the pH was adjusted to pH~8. The aqueous layer was extracted with dichloromethane (3x50 mL), and the organic layers were combined, washed with brine (30 mL), dried over magnesium sulfate, filtered, and concentrated to give the title compound.

## Example 47B

N-({5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 47A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.51 (s, 1H), 8.35 (d, 1H), 8.17 (d, 1H), 7.93 (d, 1H), 7.60 (d, 1H), 7.44-7.40 (m, 1H), 7.33 (dd, 3H), 7.05 (d, 2H), 6.61 (d, 1H), 6.31 (dd, 1H), 6.24 (s, 1H), 4.25 (d, 2H), 3.40 (s, 4H), 3.01 (s, 4H), 2.73 (d, J=8.2, 5H), 2.20 (s, 6H), 1.93 (d, 4H), 1.54 (s, 1H), 1.39 (s, 2H), 1.24 (s, 2H), 0.93 (s, 6H).



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## Example 48

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 48A

4-((1-methylpiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1-methylpiperidin-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 48B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 48A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.54 (s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.87-7.77 (m, 1H), 7.58 (d, 1H), 7.43 (s, 1H), 7.40-7.00 (m, 7H), 6.70-6.56 (m, 1H), 6.31 (s, 1H), 6.24 (s, 1H), 4.05 (s, 2H), 3.46-3.33 (m, 2H), 3.02 (s, 6H), 2.72 (d, 5H), 2.21 (s, 6H), 1.96 (s, 5H), 1.70-1.48 (m, 2H), 1.39 (s, 2H), 0.93 (s, 6H).

## Example 49

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 49A

6-((1,4-dioxan-2-yl)methoxy)-5-bromopyridine-3-sulfonamide

The title compound was prepared by substituting (1,4-dioxan-2-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 49B

6-((1,4-dioxan-2-yl)methoxy)-5-cyanopyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 49A for EXAMPLE 36B in EXAMPLE 36C.

## Example 49C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 49B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H

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NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 7.91 (d, 1H), 7.58 (d, 1H), 7.42 (t, 1H), 7.35 (d, 2H), 7.28 (s, 1H), 7.06 (d, 2H), 6.64 (dd, 1H), 6.29 (m, 2H), 4.40 (d, 2H), 3.90 (m, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 3.46 (m, 4H), 3.07 (s, 4H), 2.85 (m, 2H), 2.34 (m, 4H), 2.16 (m, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

## Example 50

N-({5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 49A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 7.99 (d, 1H), 7.56 (d, 1H), 7.46 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.65 (dd, 1H), 6.36 (dd, 1H), 6.22 (d, 1H), 4.34 (m, 2H), 3.88 (m, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 3.46 (m, 2H), 3.06 (s, 4H), 2.81 (s, 2H), 2.26 (m, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.38 (m, 2H), 0.93 (s, 6H).

## Example 51

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 51A

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with (2,2-dimethyltetrahydro-2H-pyran-4-yl)methanol.

## Example 51B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 51A in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 2H), 8.35 (s, 2H), 8.03 (d, 4H), 7.47-7.58 (m, 6H), 7.31-7.42 (m, 6H), 7.04 (d, 4H), 6.68 (dd, 2H), 6.40 (s, 2H), 6.20 (d, 2H), 3.96-4.09 (m, 2H), 3.54-3.68 (m, 2H), 3.09 (s, 4H), 2.83 (s, 2H), 2.09-2.37 (m, 7H), 1.96 (s, 2H), 1.55-1.69 (m, 2H), 1.39 (t, 2H), 1.19 (m, 8H), 0.92 (s, 6H).

## Example 52

N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 52A

3-cyano-4-fluorobenzene sulfonamide

3-Cyano-4-fluorobenzene-1-sulfonyl chloride (1.1 g) in 1,4-dioxane (10 mL) at 0° C. was treated dropwise with a 7 M

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ammonia solution in methanol (3.57 mL) and stirred for 30 minutes. A small amount of solid was removed by filtration and discarded. The filtrate was concentrated, diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and triturated with diethyl ether to give the product.

**Example 52B**

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 52A for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

**Example 52C**

3-chloro-5-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

EXAMPLE 52B (0.148 g) in acetonitrile (5 mL) was treated with N-chlorosuccinimide (0.080 g), heated at 60° C. for 3 hours and filtered to remove a small amount of solid. The filtrate was concentrated and chromatographed on silica gel with 3-15% ethyl acetate in dichloromethane as eluent. The obtained solid was slurried in water, filtered, rinsed with additional water and dried under vacuum to give the product.

**Example 52D**

N-({3-chloro-5-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 52C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 11.41 (br s, 1H), 8.07 (d, 1H), 7.89 (s, 2H), 7.61 (m, 1H), 7.53 (m, 2H), 7.35 (d, 2H), 7.18 (m, 1H), 7.05 (d, 2H), 6.69 (m, 1H), 6.42 (dd, 1H), 6.18 (dd, 1H), 3.83 (m, 2H), 3.55 (t, 2H), 3.23 (m, 3H), 3.06 (m, 4H), 2.15 (m, 4H), 1.92 (m, 4H), 1.60 (m, 2H), 1.40 (m, 2H), 1.19 (m, 4H), 0.93 (s, 6H).

**Example 53**

N-({4-[(1-acetyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 53A**

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 1G.

**254****Example 53B**

N-({4-[(1-acetyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A 5 mL round-bottomed flask was charged with EXAMPLE 53A (120 mg), 1-acetyl piperidin-4-amine (28 mg), and triethylamine (0.064 mL) in dioxane (2 mL). The reaction mixture was heated to 90° C. for 24 hours. The reaction mixture was cooled to room temperature, and added to a silica gel column and purified by eluting with 0-5% methanol in dichloromethane. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (br s, 1H), 8.65 (d, 1H), 8.24 (d, 1H), 8.03 (d, 1H), 7.83 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.19 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 4.28 (d, 1H), 3.97-3.75 (m, 2H), 3.07 (br s, 4H), 2.87-2.70 (m, 4H), 2.29-2.10 (m, 6H), 2.02 (s, 3H), 2.00-1.89 (m, 4H), 1.66-1.54 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

**Example 54**

N-({2-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 54A**

2-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 2-chloro-4,5-difluorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

**Example 54**

N-({2-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 54A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.76 (s, 1H), 11.31 (s, 1H), 8.08 (d, 1H), 7.69 (d, 1H), 7.60 (d, 1H), 7.55 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 (s, 1H), 6.84 (d, 1H), 6.69 (dd, 1H), 6.45 (dd, 1H), 6.13 (d, 1H), 3.82 (dd, 2H), 3.24 (t, 2H), 3.05 (m, 6H), 2.73 (s, 2H), 2.14 (m, 6H), 1.95 (s, 2H), 1.81 (m, 1H), 1.61 (m, 2H), 1.38 (t, 2H), 1.17 (m, 2H), 0.92 (s, 6H).

**Example 55**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 2A for

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EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (br s, 1H), 8.75 (t, 1H), 8.54 (d, 1H), 8.03 (d, 1H), 7.79 (dd, 1H), 7.54-7.48 (m, 3H), 7.35 (d, 2H), 7.08-7.02 (m, 3H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.61 (t, 4H), 3.43 (q, 2H), 3.29 (m, 2H), 3.06 (br s, 4H), 2.73 (br s, 2H), 2.47 (br s, 4H), 2.18 (m, 6H), 1.95 (br s, 2H), 1.80 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 56

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 56A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 37C for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 56B

The title compound was prepared by substituting EXAMPLE 56A for EXAMPLE 36B in EXAMPLE 36C.

## Example 56C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 56B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.70 (s, 1H), 8.51 (s, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.45 (t, 1H), 7.35-7.37 (m, 3H), 7.06 (d, 2H), 6.67 (dd, 1H), 6.33 (d, 1H), 6.26 (s, 1H), 4.56 (d, 2H), 3.76-3.80 (s, 2H), 3.56-3.62 (m, 2H), 3.01-3.10 (m, 4H), 2.14-2.18 (m, 2H), 1.96 (s, 2H), 1.80-1.87 (m, 4H), 1.41 (t, 2H), 0.93 (s, 6H).

## Example 57

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 57A

5-bromo-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-morpholinoethanol for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

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## Example 57B

5-cyano-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 57A for EXAMPLE 36A in EXAMPLE 36B.

## Example 57C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 57B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 7.92 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.36 (d, 2H), 7.31 (s, 1H), 7.06 (d, 2H), 6.65 (dd, 1H), 6.31 (d, 1H), 6.27 (d, 1H), 4.59 (t, 2H), 3.59 (s, 4H), 3.08 (s, 4H), 2.89 (s, 2H), 2.65 (s, 4H), 2.16-2.18 (m, 2H), 1.97 (s, 2H), 1.41 (t, 2H), 0.93 (s, 6H).

## Example 58

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 58A

3-chloro-4-(2-(2-methoxyethoxy)ethylthio)benzenesulfonamide

In a 25 mL, microwave tube was added sodium hydride (0.6 g) in tetrahydrofuran (10 mL) to give a suspension. 2-(2-Methoxyethoxy)ethanethiol (1 g) was added slowly. After stirring for 30 minutes, 3-chloro-4-fluorobenzenesulfonamide (1.54 g) dissolved in 10 mL tetrahydrofuran was added slowly. The mixture was heated at 110° C. for 30 minutes in a Biotage Initiator microwave reactor. Water was added, the product was extracted with ether (20 mL×3), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica eluting with 0-25% ethyl acetate in hexane.

## Example 58B

3-chloro-4-(2-(2-methoxyethoxy)ethylsulfonyl)benzenesulfonamide

EXAMPLE 58A (0.15 g) was suspended in acetic acid (3 mL). Peracetic acid (0.4 mL) was added slowly. The mixture was stirred at room temperature overnight, then poured into Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, and the product precipitated. After filtration and washing with water, the product was dried under vacuum.

## Example 58C

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 58B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H

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NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.52 (s, 1H), 7.92 (d, 1H), 7.84 (m, 2H), 7.68 (m, 1H), 7.62 (d, 1H), 7.42 (t, 1H), 7.35 (d, 2H), 7.29 (m, 1H), 7.05 (d, 2H), 6.62 (dd, 1H), 6.32 (m, 1H), 6.26 (d, 1H), 3.74 (t, 2H), 3.68 (t, 2H), 3.24 (m, 2H), 3.06 (m, 5H), 3.01 (m, 4H), 2.74 (s, 2H), 2.19 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 59

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 59A

4-(2-(2-methoxyethoxy)ethylthio)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 3-chloro-4-fluorobenzenesulfonamide in EXAMPLE 58A.

## Example 59B

4-(2-(2-methoxyethoxy)ethylsulfonyl)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 59A for EXAMPLE 58A in EXAMPLE 58B.

## Example 59C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 59B for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.51 (s, 1H), 8.17 (m, 1H), 7.94 (m, 3H), 7.64 (d, 1H), 7.42 (m, 1H), 7.35 (d, 2H), 7.28 (d, 1H), 7.05 (d, 2H), 6.62 (m, 1H), 6.28 (m, 2H), 3.83 (m, 4H), 3.16 (m, 2H), 3.08 (s, 3H), 3.01 (m, 4H), 2.73 (s, 2H), 2.18 (m, 6H), 1.96 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 60

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-morpholin-4-ylcyclohexyloxy)]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 60A

Trans-4-(4-aminocyclohexyloxy)-3-nitrobenzenesulfonamide

To a solution of tert-butyl 4-hydroxycyclohexylcarbamate (0.250 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.186 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.256 g) was added as a solution in tetrahydrofuran (1 mL). The reaction was heated to 60° C. for 1.5 hours, cooled, and poured into a mixture of dichloromethane (100 mL) and water (25 mL). The aqueous layer was adjusted to pH~4 with 1N aqueous HCl and the organic

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layer was separated, washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (GraceResolv 40 g) and eluted using a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes. This solid was treated with HCl (4.0M in dioxane, 5 mL) at room temperature for 1 hour and concentrated to give the title compound.

## Example 60B

4-(trans-4-morpholinocyclohexyloxy)-3-nitrobenzenesulfonamide

To EXAMPLE 60A (0.220 g) and 1-bromo-2-(2-bromoethoxy)ethane (0.177 g) in N,N-dimethylformamide (3 mL) was added triethylamine (0.338 mL) and the reaction heated to 70° C. for 5 hours. The reaction was cooled and the resulting precipitate was removed by filtration. The reaction was concentrated and loaded onto silica gel and was eluted using a gradient of 0.5% to 7.5% methanol/dichloromethane to give the title compound.

## Example 60C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-morpholin-4-ylcyclohexyloxy)]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 60B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.62 (s, 1H), 8.23 (s, 1H), 7.99 (s, 1H), 7.96-7.88 (m, 1H), 7.54 (d, 1H), 7.48 (s, 2H), 7.34 (d, 3H), 7.04 (d, 2H), 6.72-6.58 (m, 1H), 6.37 (s, 1H), 6.21 (s, 1H), 4.69-4.47 (m, 1H), 3.66 (s, 4H), 3.05 (s, 4H), 2.76 (s, 6H), 2.22 (s, 9H), 1.96 (s, 4H), 1.39 (s, 6H), 0.92 (s, 6H).

## Example 61

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 61A

5-bromo-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)pyridine-3-sulfonamide

A mixture of EXAMPLE 36A (1.0 g), EXAMPLE 3L (0.95 g) and triethylamine (3.08 mL) in anhydrous dioxane (20 mL) was heated at 110° C. overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 2%-8% methanol/dichloromethane to give the title compound.

## Example 61B

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 61A for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$



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NMR (400 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.59 (s, 1H), 8.35 (s, 1H), 8.00 (s, 2H), 7.55 (d, 1H), 7.46 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.63 (dd, 1H), 6.49 (m, 1H), 6.36 (s, 1H), 6.20 (s, 1H), 4.05 (m, 1H), 3.94 (d, 2H), 3.28 (m, 6H), 3.01 (s, 4H), 2.72 (s, 2H), 2.16 (m, 6H), 1.93 (m, 4H), 1.80 (m, 4H), 1.57 (m, 2H), 1.38 (t, 2H), 1.17 (t, 2H), 0.90 (s, 6H).

**Example 62**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 62A**

4-(2-cyanoethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-amino-propanenitrile for EXAMPLE 39B in EXAMPLE 39C.

**Example 62B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 62A for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (501 MHz, pyridine- $d_5$ )  $\delta$  13.04 (s, 1H), 9.24 (d, 1H), 9.04 (t, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.13 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (ddd, 2H), 7.07 (ddd, 2H), 7.02 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 6.48 (dd, 1H), 3.83 (q, 2H), 3.07 (d, 4H), 2.98 (t, 2H), 2.77 (s, 2H), 2.26 (s, 2H), 2.11-2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 63**

Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 15H for EXAMPLE 3J and EXAMPLE 39C for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (501 MHz, pyridine- $d_5$ )  $\delta$  13.09 (s, 1H), 9.30 (d, 1H), 8.64 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.10 (d, 1H), 7.68 (dt, 2H), 7.46 (ddd, 2H), 7.12 (ddd, 2H), 6.91 (d, 1H), 6.72 (dd, 1H), 6.51 (dd, 1H), 6.49 (d, 1H), 5.69 (s, 2H), 4.40 (s, 2H), 3.69-3.73 (m, 4H), 3.68 (s, 1H), 2.95-3.02 (m, 4H), 2.84 (s, 2H), 2.40-2.46 (m, 4H), 2.21 (s, 2H), 2.08-2.15 (m, 5H), 1.76-1.84 (m, 2H), 1.55-1.63 (m, 6H), 1.29 (s, 6H).

**Example 64**

Trans-N-({4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl}amino)-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 64A**

tert-butyl (trans)-4-(bis(cyclopropylmethyl)amino)cyclohexylcarbamate

The title compound was prepared by substituting cyclopropanecarbaldehyde for 4'-chlorobiphenyl-2-carboxaldehyde

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and tert-butyl (trans)-4-aminocyclohexylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

**Example 64B**

(trans)- $\text{N}^1, \text{N}^1$ -bis(cyclopropylmethyl)cyclohexane-1,4-diamine dihydrochloride

To a solution of EXAMPLE 64A (1.4 g) in dichloromethane (10 ml) was added hydrogen chloride (10 ml, 4M in dioxane) and the reaction was stirred for 16 hours at room temperature. The reaction mixture was diluted with ether and pure product was filtered off.

**Example 64C**

Trans-4-(4-(bis(cyclopropylmethyl)amino)cyclohexylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 64B for EXAMPLE 39B in EXAMPLE 39C.

**Example 64D**

Trans-N-({4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl}amino)-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 64C for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.06 (s, 1H), 9.30 (d, 1H), 8.44 (d, 1H), 8.41 (dd, 1H), 8.37 (d, 1H), 8.12 (d, 1H), 7.67 (d, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.00 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 3.36-3.43 (m, 1H), 3.02-3.09 (m, 4H), 2.87-2.94 (m, 1H), 2.77 (s, 2H), 2.47 (d, 4H), 2.25 (t, 2H), 2.11-2.16 (m, 4H), 2.08 (d, 2H), 1.97 (s, 2H), 1.84 (d, 2H), 1.39 (t, 2H), 1.26-1.35 (m, 4H), 0.90-0.98 (m, 8H), 0.50-0.56 (m, 4H), 0.18-0.23 (m, 4H).

**Example 65**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 65A**

4-((1-methylpiperidin-4-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-aminomethyl-1-methyl piperidine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 65B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 65A for EXAMPLE 130C in EXAMPLE 130D.  $^1\text{H}$  NMR (500 MHz, dichloromethane- $d_2$ )  $\delta$  9.57 (bs, 1H),

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8.78 (d, 1H), 8.41 (d, 1H), 8.14 (d, 1H), 7.90 (m, 2H), 7.64 (d, 1H), 7.45 (d, 1H), 7.23 (d, 2H), 6.95 (d, 2H), 6.76 (d, 1H), 6.59 (dd, 1H), 6.51 (d, 1H), 6.09 (d, 1H), 3.21 (m, 2H), 3.08 (m, 4H), 3.02 (m, 2H), 2.74 (s, 2H), 2.33 (s, 3H), 2.21-2.17 (m, 6H), 2.16-2.02 (m, 3H), 1.97 (br.s, 2H), 1.78 (m, 4H), 1.41 (t, 2H), 0.94 (s, 6H).

**Example 66**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 66A**

tert-butyl 3-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)morpholine-4-carboxylate for (tetrahydro-pyran-4-yl)methylamine in EXAMPLE 1F.

**Example 66B**

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 66A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1F, with the exception that the product was purified on a silica gel column eluted with 4% methanol in dichloromethane.

**Example 66C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A solution of EXAMPLE 66B in 50% trifluoroacetic acid and dichloromethane mixture was stirred at ambient temperature for 2 hours. The solvents were evaporated and the residue was purified on a reverse phase HPLC using a gradient of 20-80% acetonitrile in water containing 10 mM ammonium acetate. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (s, 1H), 8.52 (bs, 1H), 8.49 (d, 1H), 7.98 (d, 1H), 7.78 (d, 1H), 7.54 (d, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 7.34 (d, 2H), 7.04 (m, 3H), 6.65 (dd, 1H), 6.34 (s, 1H), 6.21 (d, 1H), 3.89 (d, 1H), 3.76 (d, 1H), 3.55-3.46 (m, 2H), 3.40-3.35 (m, 4H), 3.04 (m, 4H), 2.91 (t, 1H), 2.73 (s, 2H), 2.20-2.12 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

**Example 67**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE

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1F with EXAMPLE 15H and EXAMPLE 6A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 9.04 (s, 1H), 8.44 (d, 1H), 7.97 (d, 1H), 7.76 (dd, 1H), 7.49 (m, 4H), 7.38 (d, 2H), 7.14 (d, 2H), 6.64 (dd, 1H), 6.34 (d, 1H), 6.21 (d, 1H), 4.12 (s, 2H), 3.03 (m, 6H), 2.85 (m, 5H), 2.29 (m, 4H), 2.18 (m, 6H), 1.20 (s, 6H).

**Example 68**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 68A**

4-morpholinobut-2-yn-1-ol

To a solution of morpholine (4.36 g) in toluene (15 mL) was added 4-chlorobut-2-yn-1-ol (2.09 g) in toluene (5 mL). The solution was stirred at 85° C. for 3 hours. After cooling, the solid was filtered off. The filtrate was subjected to vacuum distillation to give the pure title compound.

**Example 68B**

4-(4-morpholinobut-2-ynyloxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 68A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

**Example 68C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyloxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 68B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.36 (s, 1H), 8.08 (d, 1H), 8.03 (d, 1H), 7.47-7.53 (m, 4H), 7.35 (d, 5.15 (s, 2H), 3.52-3.55 (m, 4H), 3.09 (s, 4H), 2.84 (br s, 2H), 2.23-2.40 (m, 6H), 2.12-2.18 (m, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

**Example 69**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 69A**

6-(((tetrahydro-2H-pyran-4-yl)methoxy)-5-((triisopropylsilyl)ethynyl)pyridine-3-sulfonamide

EXAMPLE 36B (0.176 g), bis(triphenylphosphine)palladium(II) chloride (0.176 g), copper(I) iodide (0.010 g), N,N-dimethylacetamide (2.5 mL) and triethylamine (0.105 mL) were combined, flushed with nitrogen and stirred for 2 minutes. (Triisopropylsilyl)acetylene (0.135 mL) was added and

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the reaction mixture was flushed with nitrogen again, heated at 60° C. overnight, diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 10-30% ethyl acetate in hexanes as the eluent to give the product.

## Example 69B

5-ethynyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 69A (0.205 g) in tetrahydrofuran (3 mL) at ambient temperature was treated with tetrabutyl ammonium fluoride (1 M in tetrahydrofuran, 0.906 mL) and stirred at ambient temperature for 4 hours. Additional tetrabutyl ammonium fluoride (1 M in tetrahydrofuran, 1.8 mL) was added and the mixture was heated at 40° C. for 45 minutes. Solid tetrabutyl ammonium fluoride (0.253 g) was added and heating was continued for 30 minutes. The reaction mixture was concentrated and then chromatographed on silica gel using 0-2% methanol in dichloromethane as the eluent to give the product.

## Example 69

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 69B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.58 (d, 1H), 8.19 (d, 1H), 8.05 (d, 1H), 7.53 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.56 (s, 1H), 4.24 (d, 2H), 3.87 (dd, 2H), 3.38 (m, 3H), 3.07 (m, 4H), 2.86 (m, 2H), 2.29 (m, 5H), 2.04 (m, 3H), 1.64 (dd, 2H), 1.34 (m, 4H), 0.93 (s, 6H).

## Example 70

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 70A

4-amino-3-cyanobenzenesulfonamide

3-Cyano-4-fluorobenzene-1-sulfonyl chloride (1.1 g) was dissolved in dioxane (4 mL). The solution was cooled to 0° C. and 7 mL of an ammonia (7N in methanol) solution was added. After the addition was complete, the ice bath was removed and the reaction was stirred at room temperature for 24 hours. After concentration of the reaction mixture, the crude material was purified by flash chromatography eluting with a gradient of 30-100% ethyl acetate/hexanes.

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## Example 70B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-amino-3-cyanophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 70A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.

## Example 70C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-amino-3-carbamoylphenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

To a solution of EXAMPLE 70B (90 mg) in ethanol (2 mL) was added tetrahydrofuran (2 mL), hydrogen peroxide (30%, 1 mL) and 1M sodium hydroxide solution (0.48 mL), followed by an additional 2 mL of tetrahydrofuran. The reaction was heated to 45° C. for 30 minutes, cooled, and then quenched with 5% HCl solution and extracted twice with dichloromethane. The extracts were combined and concentrated to obtain the product.

## Example 70D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 70C (80 mg) was combined with trimethyl orthoformate (2.3 mL) and trifluoroacetic acid (0.03 mL) and the resulting solution was stirred at room temperature for 4 hours. The mixture was purified by flash chromatography, eluting with a gradient of 3-10% methanol/dichloromethane. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 12.61 (s, 1H), 11.71 (s, 1H), 8.65 (d, 1H), 8.24 (s, 1H), 8.17 (dd, 1H), 8.04 (m, 1H), 7.73 (d, 1H), 7.57 (d, 1H), 7.51 (m, 2H), 7.39 (d, 2H), 7.07 (d, 2H), 6.70 (dd, 1H), 6.40 (m, 1H), 6.24 (br s, 1H), 3.61 (m, 6H), 3.03 (m, 2H), 2.75 (m, 2H), 2.17 (m, 2H), 2.01 (m, 2H), 1.44 (m, 2H), 0.94 (s, 6H).

## Example 71

Trans-4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-([4-((4-morpholin-4-ylcyclohexyl)amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 71A

8-chlorospiro[4.5]dec-7-ene-7-carbaldehyde

To a solution of N,N-dimethylformamide (2.81 mL) in dichloromethane (40 mL) was added dropwise POCl<sub>3</sub> (2.78 mL) at 0° C. The reaction mixture was warmed up to room temperature and spiro[4.5]decan-8-one (3.95 g) in dichloromethane (5 mL) was added dropwise. The mixture was stirred overnight. The reaction was quenched with cold aqueous sodium acetate and the resulting mixture was extracted with ether and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

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## Example 71B

8-(4-chlorophenyl)spiro[4.5]dec-7-ene-7-carbaldehyde

To a suspension of EXAMPLE 71A (3 g) in water (50 mL) was added 4-chlorophenylboronic acid (2.83 g), tetrabutylammonium (4.87 g), potassium carbonate (6.26 g) and palladium(II) acetate (0.169 g). The reaction mixture was stirred at 45°C. for 5 hours and extracted with dichloromethane. The organic layer was concentrated and the residue was loaded onto a silica gel column, and eluted with 5-20% ethyl acetate in hexane to give the title compound.

## Example 71C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 71B (274 mg) in dichloroethane (3.5 mL) was added EXAMPLE 15F (387 mg) and sodium triacetoxyborohydride (317 mg). The reaction mixture was stirred overnight. Sodium cyanoborohydride (37.6 mg) was added and the resulting mixture stirred overnight. The reaction was quenched with water and diluted with dichloromethane. The mixture was washed with water extensively and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

## Example 71D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 3J using EXAMPLE 71C in place of EXAMPLE 3I.

## Example 71E

Trans-4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-([4-([4-morpholin-4-ylcyclohexyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 9C in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.51 (s, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.76 (d, 1H), 7.44-7.53 (m, 3H), 7.34 (d, 2H), 7.07 (d, 3H), 6.66 (dd, 1H), 6.37 (dd, 1H), 6.20 (d, 1H), 3.50-3.70 (m, 5H), 3.04 (s, 4H), 2.55-2.76 (m, 5H), 2.34-2.39 (m, 1H), 2.20 (d, 6H), 2.03 (s, 4H), 1.91 (s, 2H), 1.61 (q, 4H), 1.51 (t, 2H), 1.36-1.46 (m, 8H).

## Example 72

Cis-4-(4-([4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-([4-methoxycyclohexyl]methyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 15H and 29A in place of

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EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.45 (s, 1H), 8.59 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.54 (d, 1H), 7.47-7.52 (m, 2H), 7.37 (d, 2H), 7.13 (d, 2H), 7.08 (d, 1H), 6.68 (dd, 1H), 6.35-6.42 (m, 1H), 6.19 (d, 1H), 4.11 (s, 2H), 3.37 (s, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.07 (s, 4H), 2.83 (s, 2H), 2.17 (d, 6H), 1.81 (dd, 2H), 1.64-1.73 (m, 1H), 1.48 (dd, 2H), 1.23-1.41 (m, 4H), 1.18 (s, 6H).

## Example 73

4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-([4-([4-fluorotetrahydro-2H-pyran-4-yl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 37D in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.37 (s, 1H), 7.98-8.11 (m, 2H), 4.38 (d, 2H), 3.74-3.82 (m, 2H), 3.54-3.64 (m, 2H), 3.44 (s, 1H), 3.08 (s, 3H), 2.58-2.89 (m, 2H), 2.13-2.35 (m, 4H), 2.04 (s, 2H), 1.78-1.93 (m, 4H), 1.57-1.65 (m, 4H), 1.52 (t, 2H), 1.36-1.47 (m, 4H).

## Example 74

Trans-4-(4-([8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl)piperazin-1-yl)-N-([4-([4-methoxycyclohexyl]methyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 34B in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.39 (s, 1H), 8.58 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47-7.55 (m, 3H), 7.34 (d, 2H), 7.07 (d, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.25 (t, 2H), 3.22 (s, 3H), 3.06 (s, 5H), 2.71 (s, 2H), 2.21 (s, 6H), 1.94-2.06 (m, 4H), 1.79 (d, 2H), 1.57-1.65 (m, 5H), 1.51 (t, 2H), 1.39 (t, 4H), 0.95-1.11 (m, 4H).

## Example 75

4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-([tetrahydro-2H-pyran-4-ylmethyl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 75A

methyl 5,5-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

The title compound was prepared by substituting 4,4-dimethyl-2-methoxycarbonylcyclohexanone for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 3A.

## Example 75B

methyl 2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 75A for EXAMPLE 3A in EXAMPLE 3B.



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## Example 75C

(2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methanol

The title compound was prepared by substituting EXAMPLE 75B for EXAMPLE 3B in EXAMPLE 3C.

## Example 75D

2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarbaldehyde

To a solution of EXAMPLE 75C (2.8 g) in dichloromethane (50 mL) was added Dess-Martin Periodinane (5.68 g). The reaction mixture was stirred at room temperature for 3 hours and diluted with ether and washed with 5% NaOH and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography using 20% ethyl acetate in hexanes to provide the title compound.

## Example 75E

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by replacing 4'-chlorobiphenyl-2-carboxaldehyde with EXAMPLE 75D and tert-butyl piperazine-1-carboxylate with EXAMPLE 15F in EXAMPLE 1A.

## Example 75F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 15H by replacing EXAMPLE 15G with EXAMPLE 75E.

## Example 75G

4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 75F and EXAMPLE 1F in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47-7.55 (m, 3H), 7.31-7.36 (m, 2H), 7.05-7.13 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.18 (d, 1H), 3.85 (dd, 2H), 3.22-3.31 (m, 4H), 3.07 (s, 4H), 2.67-2.78 (m, 2H), 2.19 (s, 6H), 1.82-1.98 (m, 3H), 1.56-1.66 (m, 2H), 1.39 (t, 2H), 1.17-1.33 (m, 3H), 0.93 (s, 6H).

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## Example 76

4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 75F and EXAMPLE 36C in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.62 (s, 1H), 8.73 (s, 1H), 8.52 (s, 1H), 7.98 (d, 1H), 7.56 (d, 1H), 7.45-7.51 (m, 1H), 7.43 (s, 1H), 7.37 (d, 2H), 7.10 (d, 2H), 6.68 (dd, 1H), 6.35 (dd, 1H), 6.25 (s, 1H), 4.29 (d, 2H), 3.88 (dd, 2H), 3.12 (d, 4H), 2.21 (s, 2H), 2.00-2.11 (m, 1H), 1.95 (s, 2H), 1.64 (dd, 2H), 1.27-1.46 (m, 4H), 0.95 (s, 6H).

## Example 77

tert-butyl 3-([4-([4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl]-2-nitrophenoxy)methyl)morpholine-4-carboxylate

## Example 77A

tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with tert-butyl 3-(hydroxymethyl)morpholine-4-carboxylate.

## Example 77B

tert-butyl 3-([4-([4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl]-2-nitrophenoxy)methyl)morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 77A in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.36 (s, 1H), 8.01-8.11 (m, 2H), 7.47-7.61 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.20 (s, 1H), 4.41-4.52 (m, 2H), 4.15-4.28 (m, 1H), 3.59-3.95 (m, 3H), 3.51 (d, 1H), 3.34-3.43 (m, 1H), 3.10 (s, 5H), 2.84 (s, 2H), 2.28 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.20-1.45 (m, 12H), 0.92 (s, 6H).

## Example 78

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(morpholin-3-ylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 77B (100 mg) in dichloromethane (10 mL) at 0° C. was treated with trifluoroacetic acid (5 mL) for 20 minutes. The reaction mixture was concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 35-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The

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trifluoroacetic acid salt was dissolved in dichloromethane (10 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.90 (dd, 1H), 7.57 (d, 1H), 7.42-7.46 (m, 1H), 7.31-7.37 (m, 3H), 7.25 (d, 1H), 7.01-7.09 (m, 2H), 6.64 (dd, 1H), 6.29-6.37 (m, 1H), 6.24 (d, 1H), 4.17-4.31 (m, 2H), 3.90-4.05 (m, 1H), 3.77-3.85 (m, 1H), 3.45-3.59 (m, 4H), 2.94-3.13 (m, 6H), 2.76 (s, 2H), 2.18 (d, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 79

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 1F in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.77-7.84 (m, 1H), 7.45-7.56 (m, 3H), 7.34 (d, 2H), 7.04-7.13 (m, 3H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.85 (dd, 2H), 3.22-3.31 (m, 4H), 3.07 (s, 4H), 2.71 (s, 2H), 2.21 (s, 6H), 2.03 (s, 2H), 1.81-1.94 (m, 1H), 1.56-1.68 (m, 6H), 1.51 (t, 2H), 1.34-1.45 (m, 4H), 1.20-1.33 (m, 2H).

## Example 80

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 1-(methylsulfonyl)piperidin-4-amine for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (br s, 1H), 8.57 (d, 1H), 8.25 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 3.80 (m, 1H), 3.57 (m, 2H), 3.08 (br s, 4H), 2.95 (td, 2H), 2.92 (s, 3H), 2.85-2.72 (m, 2H), 2.30-2.10 (m, 6H), 2.07-1.93 (m, 4H), 1.70 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 81

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxido-tetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 81A

1,1-Dioxotetrahydro-2H-thiopyran-4-amine

N-Benzyl-1,1-dioxotetrahydro-2H-thiopyran-4-amine (2.00 g) was added to ethanol (40 mL) in a pressure bottle. Palladium hydroxide on carbon (0.587 g) was added and the solution was stirred under 30 psi of hydrogen at room temperature for 2 hours. The mixture was filtered through a nylon membrane and the solvent was removed under vacuum.

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## Example 81B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxido-tetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 81A for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (br s, 1H), 8.55 (d, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.86 (dd, 1H), 7.52-7.47 (m, 3H), 7.35 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.21 (d, 1H), 4.05 (m, 1H), 3.22-3.00 (m, 8H), 2.79 (br s, 2H), 2.31-2.11 (m, 10H), 1.96 (br s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 82

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (br s, 1H), 8.38 (br s, 1H), 7.96 (d, 1H), 7.91 (d, 1H), 7.68 (d, 1H), 7.58 (d, 1H), 7.46 (t, 1H), 7.39-7.35 (m, 3H), 7.07 (d, 2H), 6.67 (dd, 1H), 6.34 (m, 1H), 6.28 (d, 1H), 3.31 (br s, 2H), 3.17 (br s, 8H), 2.18 (m, 2H), 1.98 (br s, 2H), 1.42 (t, 2H), 0.94 (s, 6H).

## Example 83

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 83A

3-Nitro-4-[1-(2,2,2-trifluoro-ethyl)-piperidin-4-ylamino]-benzenesulfonamide

The title compound was prepared by substituting 1-(2,2,2-trifluoroethyl)piperidin-4-amine hydrochloride for (tetrahydro-2H-pyran-4-yl)methylamine in EXAMPLE 6A.

## Example 83B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 82A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (br s, 1H), 8.56 (d, 1H), 8.24 (d, 1H), 8.04 (d, 1H), 7.81 (dd, 1H), 7.52 (dd, 2H), 7.48 (d, 1H), 7.35 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.68 (m, 1H), 3.22 (q, 2H), 3.07 (br s,

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4H), 2.90 (m, 2H), 2.75 (br s, 2H), 2.29-2.12 (m, 8H), 1.97-1.86 (m, 4H), 1.63 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Example 84

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 84A

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ol

Piperidin-4-ol (7.8 g) and dihydro-2H-pyran-4(3H)-one (5.0 g) were dissolved in titanium(IV) isopropoxide (30 mL) and the reaction was stirred at room temperature overnight. Methanol (40 mL) was added and the reaction was cooled to 0° C. Then NaBH<sub>4</sub> (3.8 g) was added in portions over one hour. After 2 hours 1N aqueous NaOH was added, followed by ethyl acetate addition. After filtration through celite the layers were separated, the aqueous layer extracted with ethyl acetate, and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The crude was purified by column chromatography using dichloromethane having 5-10% 7N NH<sub>3</sub> in methanol.

Example 84B

5-bromo-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 84A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

Example 84C

5-cyano-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 84B for EXAMPLE 36B in EXAMPLE 36C.

Example 84D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 84C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.60 (d, 1H), 8.37 (d, 1H), 7.90 (d, 1H), 7.60 (d, 1H), 7.42 (dd, 1H), 7.35 (d, 2H), 7.25 (d, 1H), 7.04 (d, 2H), 6.63 (dd, 1H), 6.28 (m, 1H), 6.24 (d, 1H), 5.30 (br s, 1H), 4.50 (d, 2H), 3.95 (dd, 2H), 3.30 (m, 5H), 3.02 (br s, 4H), 2.95 (br s, 2H), 2.24 (br s, 4H), 2.17 (br m, 4H), 1.96 (s, 2H), 1.90 (br m, 4H), 1.60 (br m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

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Example 85

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 85A

5-isopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 36B (0.176 g), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.041 g), and palladium(II) acetate (0.011 g) were combined in a 10 mL oven-dried flask. Tetrahydrofuran (1 mL) was added and the mixture was flushed with nitrogen and stirred at ambient temperature for 5 minutes. 2-Propylzinc bromide solution (0.5 M in tetrahydrofuran) (1.5 mL) was added and stirring was continued under nitrogen overnight. Additional 2,2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.041 g) and palladium(II) acetate (0.011 g) were added. The mixture was flushed with nitrogen and stirred at ambient temperature for 5 minutes. 2-Propylzinc bromide solution (0.5 M in tetrahydrofuran) (1.5 mL) was added and stirring was continued under nitrogen for 2.5 days. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated, and chromatographed on silica gel with 0 to 3% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent. The obtained material was chromatographed on silica gel a second time with 10-40% ethyl acetate in CH<sub>2</sub>Cl<sub>2</sub> as the eluent, triturated with diethyl ether and dried under vacuum at 45° C. to give the product.

Example 85B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 85A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 8.49 (m, 1H), 8.04 (d, 1H), 7.90 (m, 1H), 7.57 (m, 1H), 7.52 (t, 1H), 7.48 (dd, 1H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.17 (s, 1H), 4.19 (m, 2H), 3.88 (m, 2H), 3.30 (m, 2H), 3.05 (m, 5H), 2.77 (s, 2H), 2.21 (s, 4H), 2.14 (s, 2H), 2.03 (m, 1H), 1.95 (s, 2H), 1.64 (m, 2H), 1.34 (m, 4H), 1.12 (d, 6H), 0.92 (s, 6H).

Example 86

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 86A

3-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 3,4-difluorobenzenesulfonamide for 4-chloro-3-nitrobenzene-

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sulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 86B

3-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 86A for EXAMPLE 52B in EXAMPLE 52C.

## Example 86C

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 86B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.72 (s, 1H), 11.20 (s, 1H), 8.08 (d, 1H), 7.61 (m, 2H), 7.50 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.42 (dd, 1H), 6.16 (d, 1H), 6.09 (m, 1H), 3.81 (dd, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.76 (s, 2H), 2.18 (m, 6H), 1.95 (s, 2H), 1.72 (m, 1H), 1.53 (d, 2H), 1.38 (t, 2H), 1.16 (m, 2H), 0.92 (s, 6H).

## Example 87

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

## Example 87A

methyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

The title compound was prepared by substituting 5-hydroxyindole for EXAMPLE 3G in EXAMPLE 3H.

## Example 87B

methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 87A for EXAMPLE 3H in EXAMPLE 3I.

## Example 87C

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 87B for EXAMPLE 3I in EXAMPLE 3J.

## Example 87D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 1E in EXAMPLE 1G,

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except here the crude was purified by preparative HPLC using a 250×50 mm C18 column and eluting with 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.40 (br s, 1H), 11.17 (s, 1H), 9.50 (v br s, 1H), 8.61 (t, 1H), 8.57 (d, 1H), 7.77 (dd, 1H), 7.70 (br s, 1H), 7.50 (m, 5H), 7.36 (m, 5H), 7.10 (s, 1H), 7.08 (d, 1H), 6.83 (dd, 1H), 6.69 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.30 (br s, 1H), 3.84 (dd, 2H), 3.70 (br s, 1H), 3.30 (m, 6H), 3.20, 2.95, 2.80 (all br s, total 6H), 1.86 (m, 1H), 1.60 (m, 2H), 1.25 (m, 2H).

## Example 88

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 1E and EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G, except here the crude was purified by preparative HPLC using a 250×50 mm C18 column and eluting with 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.40 (br s, 1H), 11.19 (s, 1H), 9.60 (v br s, 1H), 8.69 (t, 1H), 8.60 (d, 1H), 7.83 (dd, 1H), 7.65 (br s, 1H), 7.50 (m, 5H), 7.38 (m, 5H), 7.12 (m, 2H), 6.83 (dd, 1H), 6.69 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 4.38 (br s, 1H), 4.00 (m, 2H), 3.80 (br s, 1H), 3.40 (m, 4H), 3.30-2.80 (envelope, 10H), 3.20 (m, 4H), 1.96 (m, 2H).

## Example 89

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 87C for EXAMPLE 1E and EXAMPLE 3M for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.15 (s, 1H), 8.56 (d, 1H), 8.20 (d, 1H), 7.84 (dd, 1H), 7.52 (d, 1H), 7.39-7.31 (m, 4H), 7.12 (d, 2H), 7.04 (d, 2H), 6.84 (dd, 1H), 6.65 (dd, 1H), 6.38 (t, 1H), 6.14 (d, 1H), 3.94 (m, 2H), 3.84 (m, 1H), 3.02 (m, 8H), 2.79 (m, 3H), 2.72 (s, 2H), 2.20-2.02 (m, 8H), 1.85 (m, 6H), 1.60 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 90

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 1E and EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.08 (s, 1H), 8.51 (d, 1H), 8.13 (d, 1H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.37-7.31 (m, 4H), 7.06-7.00 (m, 4H), 6.79 (dd, 1H), 6.59 (dd, 1H), 6.35 (t, 1H), 6.14 (d, 1H), 3.73 (m, 1H), 3.05-2.95 (m, 6H), 2.71 (s, 2H), 2.60 (m, 2H), 2.48 (s, 3H), 2.16 (m, 6H), 2.01 (m, 2H), 1.95 (s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).



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## Example 91

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 6A for EXAMPLE 11B and EXAMPLE 87C for EXAMPLE 3J in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.14 (s, 1H), 9.18 (s, 1H), 8.53 (d, 1H), 7.84 (dd, 1H), 7.56 (d, 1H), 7.51 (d, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.12 (d, 1H), 7.03 (d, 2H), 6.84 (dd, 1H), 6.62 (dd, 1H), 6.38 (m, 1H), 6.13 (d, 1H), 3.00 (m, 4H), 2.90 (m, 4H), 2.71 (s, 2H), 2.33 (s, 3H), 2.15 (m, 6H), 1.94 (s, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

## Example 92

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl]-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 87C and EXAMPLE 12A in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38-7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20-4.28 (m, 2H), 3.85-3.91 (m, 1H), 3.82 (dd, 1H), 3.74-3.78 (m, 1H), 3.59-3.69 (m, 2H), 3.40-3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 93

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 3J and EXAMPLE 16A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.17 (s, 1H), 8.18 (d, 1H), 7.92 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.26 (m, 1H), 7.17 (d, 1H), 7.04 (m, 3H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.14 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.03 (s, 4H), 2.74 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 94

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 3J and EXAMPLE 17A for

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EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.20 (s, 1H), 8.19 (d, 1H), 7.90 (dd, 1H), 7.53 (d, 1H), 7.40 (m, 4H), 7.33 (t, 1H), 7.17 (d, 1H), 7.07 (m, 3H), 6.86 (dd, 1H), 6.70 (dd, 1H), 6.41 (s, 1H), 6.21 (d, 1H), 3.84 (dd, 2H), 3.59 (m, 2H), 3.25 (m, 6H), 3.00 (m, 2H), 2.74 (s, 2H), 2.54 (m, 2H), 2.18 (s, 2H), 2.01 (s, 2H), 1.83 (m, 1H), 1.54 (m, 2H), 1.45 (t, 2H), 1.23 (m, 2H), 0.94 (s, 6H).

## Example 95

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 95A

1-(1,3-difluoropropan-2-yl)piperidin-4-amine

Tert-butyl piperidin-4-ylcarbamate (0.212 g), 1,3-difluoropropan-2-one (0.149 g) and sodium triacetoxyborohydride (0.337 g) were stirred together in dichloroethane at room temperature. After stirring overnight the reaction was quenched with water (10 mL) and extracted into dichloromethane (2×20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was treated with hydrogen chloride (4.0M in dioxane, 1.323 mL) for 1 hour to give the title compound as the HCl salt after concentration.

## Example 95B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 95A (0.057 g) and EXAMPLE 53A (0.162 g) were suspended in dioxane (3 mL) and heated to 105° C. overnight. The reaction was concentrated, loaded onto silica gel (GraceResolv 12 g) and eluted with a gradient of 0.5% to 4% methanol/dichloromethane. The product containing fractions were concentrated and loaded onto C18 (SF25-75 g analogix column) and eluted using a gradient of 30% to 60% acetonitrile/water. The product was partitioned between dichloromethane (20 mL) and saturated aqueous NaHCO<sub>3</sub> solution (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.10 (s, 1H), 8.88 (d, 2H), 8.45 (d, 1H), 8.20 (s, 1H), 8.18-8.09 (m, 1H), 7.95 (d, 1H), 7.68 (d, 1H), 7.44 (s, 1H), 7.23-7.19 (m, 1H), 6.91 (d, 3H), 6.53 (d, 2H), 5.98 (d, 1H), 4.64 (dd, 4H), 3.68-3.50 (m, 1H), 3.01 (d, 6H), 2.72 (d, 4H), 2.19 (s, 11H), 1.69 (s, 2H), 1.41 (s, 2H), 0.94 (s, 6H).

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## Example 96

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 96A

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 96B

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 96A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 8.03 (d, 1H), 7.56 (d, 1H), 7.50 (m, 2H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.22 (s, 1H), 4.50 (d, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.12 (v br s, 4H), 2.93 (v br s, 2H), 2.38 (v br s, 4H), 2.17 (br m, 2H), 1.96 (s, 2H), 1.86 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

## Example 97

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 97A

tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 4-aminopiperidine-1-carboxylate for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 97B

3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide

Tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate was dissolved in dichloromethane (3 mL) and treated with 1N HCl in ether (4 mL). The reaction was stirred overnight then concentrated to give the title compound.

## Example 97C

4-(1-(2,2-difluoroethyl)piperidin-4-ylamino)-3-nitrobenzenesulfonamide

3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide hydrochloride (0.100 g), 1,1-difluoro-2-iodoethane (0.063

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mL) and diisopropylamine (0.156 mL) were stirred together in N,N-dimethylformamide (3 mL) and heated to 85° C. The reaction was diluted with dichloromethane (50 mL) and washed with water (50 mL), brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (GraceResolve 12 g) and eluted using a gradient of 0.5% methanol/dichloromethane to 3% methanol/dichloromethane over 30 minutes to give the title compound.

## Example 97D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 97B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.54-11.27 (m, 1H), 8.55 (d, 1H), 8.24 (d, 1H), 8.03 (d, 1H), 7.81 (d, 1H), 7.50 (dd, 3H), 7.34 (d, 2H), 7.13 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.38 (dd, 1H), 6.15 (dt, 2H), 3.64 (s, 1H), 3.07 (s, 4H), 2.79 (ddd, 6H), 2.41 (t, 2H), 2.17 (d, 6H), 1.92 (d, 4H), 1.61 (d, 2H), 1.38 (s, 2H), 0.92 (s, 6H).

## Example 98

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[1-(cyclopropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiperidin-4-amine with 4-amino-1-cyclopropylpiperidine. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.54 (d, 1H), 8.22 (d, 1H), 8.02 (d, 1H), 7.80 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.11 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.69 (m, 1H), 3.06 (m, 4H), 2.92 (m, 2H), 2.74 (s, 2H), 2.23 (m, 7H), 1.93 (m, 5H), 1.77 (m, 1H), 1.55 (m, 3H), 1.38 (t, 2H), 0.92 (s, 6H), 0.43 (m, 4H).

## Example 99

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[1-(morpholin-4-yl)cyclohexyl]methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiperidin-4-amine with 1-(4-morpholino)cyclohexanemethylamine. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 9.06 (s, 1H), 8.59 (d, 1H), 8.06 (d, 1H), 7.83 (dd, 1H), 7.57 (d, 1H), 7.50 (m, 2H), 7.34 (m, 3H), 7.19 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.17 (d, 1H), 3.56 (m, 6H), 3.44 (m, 2H), 3.07 (m, 5H), 2.57 (m, 5H), 2.24 (m, 6H), 1.95 (s, 3H), 1.45 (m, 6H), 1.23 (m, 3H), 0.92 (s, 6H).

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**279****Example 100**

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 100A**

Trans-tert-butyl-4-(dicyclopropylamino)cyclohexylcarbamate

A suspension of trans-tert-butyl-4-aminocyclohexylcarbamate (1 g), molecular sieves 3A (1 g), acetic acid (2.67 ml), (1-ethoxycyclopropoxy)trimethylsilane (3.74 ml) and sodium cyanoborohydride (0.880 g) in dry methanol (10 ml) was heated at reflux for 3 hours. The insolubles were filtered off, the resulting solution was basified with aqueous NaOH (6 M) to pH 14, and extracted with ether. The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography (silica gel 80 g, 30-100% acetone/hexanes) to provide the title compound.

**Example 100B**

(trans)-N<sup>1</sup>,N<sup>1</sup>-dicyclopropylcyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 100A for EXAMPLE 39A in EXAMPLE 39B.

**Example 100C**

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(dicyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A suspension of EXAMPLE 53A (0.14 g), EXAMPLE 100B (0.112 g) and N,N-diisopropylethylamine (0.310 mL) in dioxane (10 mL) was stirred for 3 days at 100° C. The product was concentrated and purified by RP HPLC (C8, 30%-100% CH<sub>3</sub>CN/water/0.1% trifluoroacetic acid). <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.28 (d, 1H), 8.41-8.45 (m, 2H), 8.37 (d, 1H), 8.12 (d, 1H), 7.67 (d, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.01 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48-6.51 (m, 1H), 3.43 (ddd, 1H), 3.03-3.09 (m, 4H), 2.72-2.79 (m, 3H), 2.22-2.28 (m, 2H), 2.11-2.16 (m, 4H), 2.10 (s, 2H), 2.00-2.05 (m, 2H), 1.97 (s, 2H), 1.89 (s, 1H), 1.86 (s, 3H), 1.62-1.71 (m, 2H), 1.39 (t, 2H), 1.19-1.29 (m, 2H), 0.93 (s, 6H), 0.48 (d, 8H).

**Example 101**

4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 101A****Ethyl**

2-hydroxy-6,6-dimethylcyclohex-1-enecarboxylate

Into a 500 mL flame dried round-bottomed flask was added copper(I) iodide (18 g) in ether (200 mL) to give a suspension.

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After cooling to -5° C., methyllithium (120 mL, 1.6M in ether) was added dropwise. After stirring at -5° C. for 1 hour, 3-methylcyclohex-2-enone (5.15 mL) in 15 ml ether was added dropwise, and the mixture was stirred at -5° C. for 1 hour. After cooling to -78° C., hexamethylphosphoramide (60 mL) was added dropwise. Ethyl carbonocyanidate (23.74 mL) was added. After stirring at -78° C. for 20 minutes, the mixture was warmed up to room temperature, and stirred for 1 hour. The mixture was poured into cold water, and the layers were separated. The aqueous layer was extracted with ether (3×20 mL). The combined organic layers were washed with saturated aqueous NH<sub>4</sub>Cl (3×20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and dried under vacuum. The crude product was added to a silica gel column and purified by eluting with 0-10% ethyl acetate in hexane.

**Example 101B**

Ethyl 6,6-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

Into a 500 mL round-bottomed flask was added hexane-washed sodium hydride (0.5 g) in dichloromethane (100 mL) to give a suspension. After cooling to -5° C., EXAMPLE 101A (2.0 g) was added. After stirring at -5° C. for 30 minutes, the mixture was cooled to -78° C. Trifluoromethanesulfonic anhydride (2.2 mL) was added. The mixture was warmed to room temperature and stirred overnight. Water was added slowly to the mixture, the aqueous layer was then extracted by dichloromethane (2×20 mL). The combined organic layers were washed with saturated NH<sub>4</sub>Cl and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated.

**Example 101C**

ethyl 2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enecarboxylate

Into a 25 mL microwave tube was added EXAMPLE 101B (2.9 g), 4-chlorophenylboronic acid (2.2 g), and tetrakis(triphenylphosphine)palladium (0.05 g) in 1,2-dimethoxyethane/methanol (2:1, 10 mL) to give a solution. Cesium fluoride (4 g) was then added. The reaction mixture was stirred at 150° C. under (100 W) in a Biotage Initiator microwave reactor for 30 minutes. After removing the solvents, water was added, and the mixture was extracted with ethyl acetate (2×). The combined organic layers were dried by MgSO<sub>4</sub>. After filtering, the crude product was purified by reverse phase chromatography eluting with 50-100% acetonitrile/water with 0.1% trifluoroacetic acid.

**Example 101D**

(2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methanol

In a 100 mL, round-bottomed flask was placed lithium aluminum hydride (1 g) in ether (20 mL) to give a suspension. EXAMPLE 101C (1 g) dissolved in ether (5 mL) was added slowly by syringe. The mixture was stirred at room temperature overnight. After cooling to 0° C., the reaction was quenched by water. Ether (2×10 mL) was used to extract the product. The crude product was purified by flash chromatography on silica by eluting with 0-15% ethyl acetate in hexane.

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## Example 101E

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-  
((2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)  
methyl)piperazin-1-yl)benzoate

To a 0° C. solution of EXAMPLE 101D (0.43 g) in dichlo-  
romethane (5 mL) was added triethylamine (1 mL). Methane-  
sulfonyl chloride (0.134 mL) was then added slowly. After 5  
minutes, EXAMPLE 15F (0.61 g) was added. The mixture  
was stirred at room temperature overnight. The crude product  
was purified by flash chromatography on silica with 0 to 25%  
ethyl acetate in hexanes to provide the title compound.

## Example 101F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-  
chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methyl)  
piperazin-1-yl)benzoic acid

In a 5 mL microwave tube was added lithium hydroxide  
hydrate (15 mg) and EXAMPLE 101E (45 mg) in dioxane/  
water (2:1) (2 mL) to give a suspension. The mixture was  
heated to 130° C. in a Biotage Initiator microwave reactor for  
20 minutes. After cooling and neutralization by HCl, the  
crude product was added to a Prep HPLC column and was  
eluted with 20-80% acetonitrile/water with 0.1% trifluoro-  
acetic acid.

## Example 101G

4-(4-([2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-  
en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(tet-  
rahydro-2H-pyran-4-yl)methyl]amino}  
phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-  
yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 101F for EXAMPLE 3J and EXAMPLE 1F for  
EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz,  
dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.47 (s, 1H), 8.58 (m,  
2H), 8.03 (m, 1H), 7.79 (m, 1H), 7.51 (m, 3H), 7.31 (d, 2H),  
7.10 (m, 1H), 7.02 (d, 2H), 6.65 (m, 1H), 6.39 (m, 1H), 6.15  
(m, 1H), 3.85 (m, 2H), 3.27 (m, 4H), 2.97 (m, 4H), 2.76 (s,  
2H), 2.14 (m, 6H), 1.70 (m, 2H), 1.61 (m, 2H), 1.44 (m, 2H),  
1.26 (m, 3H), 1.16 (m, 6H).

## Example 102

N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]  
pyridin-3-yl}sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,  
4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-  
yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 102A

(4-ethylmorpholin-3-yl)methanol

Morpholin-3-ylmethanol (500 mg) and iodoethane (666  
mg) in N,N-dimethylformamide was treated with K<sub>2</sub>CO<sub>3</sub> (1.1  
g) overnight. The reaction mixture was diluted with water and

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extracted with ethyl acetate. The organic layer was dried over  
Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title com-  
pound.

## Example 102B

5-bromo-6-((4-ethylmorpholin-3-yl)methoxy)pyri-  
dine-3-sulfonamide

The title compound was prepared as described in  
EXAMPLE 12A by replacing 4-fluoro-3-nitrobenzene-  
sulfonamide and (1,4-dioxan-2-yl)methanol with 5-bromo-  
6-fluoropyridine-3-sulfonamide and EXAMPLE 102A,  
respectively.

## Example 102C

N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]  
pyridin-3-yl}sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,  
4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-  
yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in  
EXAMPLE 11D using EXAMPLE 102B in place of  
EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>)  
δ 11.62 (s, 1H), 8.51 (s, 1H), 8.30 (s, 1H), 8.00 (d, 1H), 7.55  
(d, 1H), 7.45-7.50 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.66  
(dd, 1H), 6.37 (s, 1H), 6.21 (d, 1H), 4.58 (dd, 1H), 4.39-4.50  
(m, 1H), 3.78-3.90 (m, 1H), 3.67-3.77 (m, 1H), 3.50-3.65 (m,  
2H), 3.08 (s, 4H), 2.59-3.00 (m, 4H), 2.20-2.39 (m, 2H), 2.15  
(s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.99-1.11 (m, 3H), 0.93 (s,  
6H)

## Example 103

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-ethylmor-  
pholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-  
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 103A

4-((4-ethylmorpholin-3-yl)methoxy)-3-nitrobenzene-  
sulfonamide

The title compound was prepared as described in  
EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol  
with EXAMPLE 102A.

## Example 103B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-ethylmor-  
pholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-  
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in  
EXAMPLE 11D using EXAMPLE 103A in place of  
EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>)  
δ 11.66 (s, 1H), 8.33 (s, 1H), 7.99-8.06 (m, 2H), 7.47-7.57 (m,  
3H), 7.45 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H),  
6.38 (dd, 1H), 6.20 (d, 1H), 4.42 (dd, 1H), 4.23 (dd, 1H), 3.81  
(d, 1H), 3.69 (d, 1H), 3.49-3.63 (m, 2H), 3.08 (s, 4H), 2.92 (s,  
1H), 2.81 (s, 4H), 2.54 (s, 1H), 2.25 (s, 4H), 2.15 (s, 2H), 1.96  
(s, 2H), 1.39 (t, 2H), 1.00 (t, 3H), 0.92 (s, 6H)



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## Example 104

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 78 (20 mg) and dihydro-2H-pyran-4(3H)-one (10 mg) in dichloroethane (2 mL) was treated with NaCNBH<sub>3</sub> (9.74 mg) overnight. Additional dihydro-2H-pyran-4(3H)-one (20 mg) and titanium (IV) isopropoxide (0.05 mL) were added. The resulting mixture was stirred at room temperature overnight and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 35-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.35 (s, 1H), 8.04 (s, 2H), 7.44-7.58 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 4.44 (s, 1H), 4.28 (s, 1H), 3.85 (d, 2H), 3.71 (d, 1H), 3.61 (s, 3H), 3.20-3.29 (m, 2H), 3.08 (s, 5H), 2.54-2.96 (m, 5H), 2.06-2.42 (m, 5H), 1.96 (s, 2H), 1.77 (d, 1H), 1.53-1.66 (m, 1H), 1.29-1.51 (m, 4H), 0.92 (s, 6H).

## Example 105

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-yl]piperidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 105A

(S)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl piperidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 105B

(S)-1-(tetrahydro-2H-pyran-4-yl)piperidin-3-amine

The title compound was prepared by substituting EXAMPLE 105A for EXAMPLE 1A in EXAMPLE 1B.

## Example 105C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-yl]piperidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 105B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 8.68 (br s, 1H), 8.54 (br s, 1H), 8.02 (d, 1H), 7.77 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 3.98 (m, 2H), 3.90 (m, 2H), 3.52 (m,

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2H), 3.09 (s, 2H), 3.05 (m, 4H), 2.77 (m, 2H), 2.60 (m, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.65 (m, 5H), 1.50 (m, 3H), 1.38 (m, 2H), 0.94 (s, 6H).

## Example 106

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 106A

5-Bromo-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting (tetrahydro-2H-pyran-4-yl)methanamine for EXAMPLE 3L in EXAMPLE 61A.

## Example 106B

5-cyano-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 106A for EXAMPLE 36B in EXAMPLE 36C.

## Example 106C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 106B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.62 (s, 1H), 8.55 (s, 1H), 8.14 (s, 1H), 8.01 (d, 1H), 7.87 (s, 1H), 7.56 (d, 1H), 7.48 (d, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (m, 1H), 6.37 (s, 1H), 6.19 (d, 1H), 3.81 (dd, 2H), 3.25 (m, 4H), 3.04 (s, 4H), 2.74 (s, 2H), 2.17 (m, 6H), 1.95 (s, 2H), 1.87 (m, 1H), 1.53 (m, 2H), 1.37 (t, 2H), 1.18 (m, 2H), 0.91 (s, 6H).

## Example 107

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 107A

3-nitro-4-(4-aminothiomorpholine-1,1-dioxide)benzenesulfonamide

The title compound was prepared by substituting 4-aminothiomorpholine-1,1-dioxide for (tetrahydropyran-4-yl)methanamine in EXAMPLE 1F.

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## Example 107B

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 107A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 9.58 (s, 1H), 8.50 (s, 1H), 8.02 (d, 1H), 7.78 (m, 2H), 7.50 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.38 (s, 1H), 6.19 (d, 1H), 3.48 (m, 4H), 3.23 (m, 4H), 3.05 (s, 4H), 2.73 (d, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 108

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 108A

4-((4-aminotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-(aminomethyl)tetrahydro-2H-pyran-4-amine for (tetrahydro-2H-pyran-4-yl)methanamine in EXAMPLE 1F.

## Example 108B

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 108A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.55 (s, 1H), 8.45 (s, 2H), 7.95 (d, 1H), 7.75-7.77 (m, 1H), 7.57 (d, 2H), 7.44 (s, 1H), 7.34 (d, 2H), 7.09 (d, J=8.85 Hz, 1H), 7.05 (d, 2H), 6.69 (dd, 1H), 6.33 (d, 1H), 6.22 (d, 1H), 3.59-3.71 (m, 6H), 3.01 (s, 4H), 2.73 (s, 2H), 2.15-2.19 (m, 6H), 1.95 (s, 2H), 1.71-1.74 (m, 2H), 1.59-1.61 (m, 1H), 1.38 (t, 2H), 0.93 (s, 6H).

## Example 109

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 109A

Trans-5-bromo-6-(4-morpholinocyclohexyloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 9B for EXAMPLE 3L in EXAMPLE 61A.

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## Example 109B

Trans-5-cyano-6-(4-morpholinocyclohexylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 109A for EXAMPLE 36B in EXAMPLE 36C.

## Example 109C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 109B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.56 (d, 1H), 8.13 (s, 1H), 8.00 (d, 1H), 7.55 (d, 1H), 7.47 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.36 (d, 1H), 6.19 (d, 1H), 4.00 (m, 1H), 3.65 (m, 4H), 3.28 (m, 4H), 3.03 (m, 4H), 2.73 (m, 4H), 2.16 (m, 6H), 1.90 (m, 6H), 1.40 (m, 6H), 0.93 (s, 6H).

## Example 110

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 52B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.23 (s, 1H), 8.08 (d, 1H), 7.91 (d, 1H), 7.74 (dd, 1H), 7.60 (d, 1H), 7.52 (m, 2H), 7.34 (m, 2H), 7.16 (s, 1H), 7.04 (m, 2H), 6.83 (d, 1H), 6.68 (dd, 1H), 6.43 (dd, 1H), 6.16 (d, 1H), 3.83 (dd, 2H), 3.23 (m, 2H), 3.12 (t, 2H), 3.06 (m, 4H), 2.73 (m, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.82 (m, 1H), 1.58 (m, 2H), 1.38 (m, 2H), 1.18 (m, 2H), 0.92 (s, 6H).

## Example 111

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 111A

benzyl (1S,3R)-3-(tert-butoxycarbonylamino)cyclopentylcarbamate

(1S,3R)-3-(tert-butoxycarbonylamino)cyclopentanecarboxylic acid (1.03 g), diphenylphosphoryl azide (DPPA, 1.00 mL), triethylamine (0.929 mL), and benzyl alcohol (0.931 mL) were combined in toluene (10 mL) and stirred at 100° C. for 24 hours. The solution was cooled and chromatographed on silica gel using 10% ethyl acetate/hexanes to give the pure product.

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Example 111B

benzyl (1S,3R)-3-aminocyclopentylcarbamate

The title compound was prepared by substituting  
EXAMPLE 111A for EXAMPLE 1A in EXAMPLE 1B.

Example 111C

benzyl (1S,3R)-3-morpholinocyclopentylcarbamate

A solution of EXAMPLE 111B (400 mg), 1-bromo-2-(2-bromoethoxy)ethane (0.246 mL), and triethylamine (0.595 mL) in N,N-dimethylformamide (6 mL) was stirred at 70° C. for 24 hours. The solution was cooled and poured into ethyl acetate (200 mL). The solution was extracted with 3× water, washed with brine, concentrated, and chromatographed on silica gel using 10% methanol/ethyl acetate to give the pure product.

Example 111D

(1S,3R)-3-morpholinocyclopentanamine

EXAMPLE 111C (300 mg) and ethanol (20 ml) were added to wet 20% Pd(OH)<sub>2</sub>-C (60.0 mg) in a 50 mL pressure bottle and stirred for 8 hours at 30 psi. The mixture was filtered through a nylon membrane and condensed to give the product.

Example 111E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 111D for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.45 (d, 1H), 8.28 (dd, 1H), 7.97 (d, 1H), 7.68 (d, 1H), 7.52 (d, 1H), 7.44 (d, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.92 (dd, 1H), 6.85 (dd, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 4.08 (m, 1H), 3.60 (br s, 4H), 3.06 (br s, 4H), 2.73 (br s, 3H), 2.48 (m, 4H), 2.28 (m, 1H), 2.18 (m, 6H), 2.07 (m, 1H), 1.95 (s, 2H), 1.79 (m, 2H), 1.63 (m, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

Example 112A

tert-butyl (1R,3S)-3-aminocyclopentylcarbamate

The title compound was prepared by substituting  
EXAMPLE 111A for EXAMPLE 111C in EXAMPLE  
111D.

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Example 112B

tert-butyl  
(1R,3S)-3-morpholinocyclopentylcarbamate

The title compound was prepared by substituting  
EXAMPLE 112A for EXAMPLE 111B in EXAMPLE 111C.

Example 112C

(1R,3S)-3-morpholinocyclopentanamine

The title compound was prepared by substituting  
EXAMPLE 112B for EXAMPLE 1A in EXAMPLE 1B.

Example 112D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared by substituting  
EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 112C for  
EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (dimethylsulfoxide-d<sub>6</sub>) δ 11.35 (s, 1H), 8.51 (d, 1H), 8.44 (dd, 1H), 8.00 (d, 1H), 7.77 (d, 1H), 7.50 (d, 1H), 7.48 (s, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 7.02 (dd, 1H), 6.67 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.11 (m, 1H), 3.61 (br s, 4H), 3.06 (br s, 4H), 2.73 (br s, 3H), 2.50 (m, 4H), 2.28 (m, 1H), 2.18 (m, 6H), 2.06 (m, 1H), 1.95 (s, 2H), 1.77 (m, 2H), 1.66 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

Example 113

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 113A

tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

Example 113B

tert-butyl 2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting  
EXAMPLE 113A for EXAMPLE 1F and EXAMPLE 3J for

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EXAMPLE 1E in EXAMPLE 1G, with the exception that the product was purified on a silica gel column eluted with 4% methanol in dichloromethane.

## Example 113C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 113B for EXAMPLE 66B in EXAMPLE 66C. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.55 (br, s, 1H), 8.51 (s, 1H), 8.00 (d, 1H), 7.80 (d, 1H), 7.52 (d, 1H), 7.49-7.46 (m, 2H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.36 (s, 1H), 6.20 (d, 1H), 4.00 (dd, 1H), 3.91 (m, 1H), 3.70 (t, 1H), 3.60 (m, 1H), 3.58 (m, 1H), 3.32 (m, 1H), 3.16 (d, 1H), 3.05 (m, 4H), 2.98 (td, 1H), 2.86 (t, 1H), 2.73 (s, 2H), 2.20-2.12 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 114

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 114A

3-nitro-4-((tetrahydrofuran-3-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 3-aminomethyl-tetrahydrofuran for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 114B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 114A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.42 (bs, 1H), 8.63 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.53-7.48 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.82-3.79 (m, 1H), 3.71 (t, 1H), 3.62 (dd, 1H), 3.50 (dd, 1H), 3.38 (m, 1H), 3.32 (m, 1H), 3.07 (m, 4H), 2.76 (s, 2H), 2.58 (m, 1H), 2.25-2.00 (m, 6H), 1.98 (m, 1H), 1.95 (s, 2H), 1.65 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 115

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 115A

Cis-tert-butyl 1-(3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

The title compound was prepared as a racemate of the cis diastereomer by substituting tert-butyl piperidin-4-ylcarbam-

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ate for piperidin-4-ol and 3-fluorodihydro-2H-pyran-4(3H)-one (prepared by the method described in US2005/0101628A1) for dihydro-2H-pyran-4(3H)-one in EXAMPLE 84A.

## Example 115B

Cis-1-(3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-amine

EXAMPLE 115A (0.29 g) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (9 mL), then 4N HCl in dioxane (4 mL) was added and the reaction stirred at room temperature for 16 hours. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL), then 4N aqueous NaOH (5 mL) was added. After shaking and separating the layers the aqueous layer was saturated with solid NaCl and extracted with more CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration the amine was used with no further purification.

## Example 115C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 115B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.54 (d, 1H), 8.43 (br d, 1H), 8.03 (d, 1H), 7.80 (dd, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.11 (d, 1H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 4.92 (d, 1H), 3.95 (m, 2H), 3.70 (v br m, 1H), 3.50, 3.40, 3.30 (all m, total 5H), 3.05, 3.00 (both v br m, total 5H), 2.74 (s, 2H), 2.55 (v br m, 1H), 2.18 (br m, 6H), 1.95 (m, 4H), 1.88 (ddd, 1H), 1.63 (v br m, 3H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 116

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 116A

1-(tetrahydro-2H-pyran-4-yl)azetidin-3-amine

Tert-butyl azetidin-3-ylcarbamate (0.46 g), dihydro-2H-pyran-4(3H)-one (0.29 g) and sodium triacetoxymethylborohydride (0.85 g) were stirred together in dichloromethane (5 mL) overnight. The reaction was poured into dichloromethane (50 mL) and saturated aqueous NaHCO<sub>3</sub> solution (25 mL). The organic layer was separated, washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane over 20 minutes gave the Boc-protected intermediate. Treatment with HCl (4.0M in dioxane, 2 mL) and methanol (1 mL) for 1 hour gave the title compound after concentration as the di-HCl salt.



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## Example 116B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)azetidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A suspension of 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-chloro-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (0.180 g), 1-(tetrahydro-2H-pyran-4-yl)azetidin-3-amine (0.078 g), and triethylamine (0.159 mL) in dioxane (2 mL) was degassed with nitrogen for 30 seconds then sealed. The reaction was heated to 110° C. After stirring for 16 hours, more triethylamine (10 equivalents total) and dimethylsulfoxide (1 mL) were added and the reaction stirred for an additional 18 hours at 110° C. The reaction was cooled, diluted with water (50 mL) and extracted with dichloromethane (2x150 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane (Flow=36 mL/minutes) gave the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.49 (d, 1H), 8.40 (s, 1H), 7.97 (d, 1H), 7.77 (s, 1H), 7.47 (dd, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90-6.78 (m, 1H), 6.65 (d, 1H), 6.35 (s, 1H), 6.21 (s, 1H), 4.47-4.23 (m, 1H), 3.83 (s, 3H), 3.05 (s, 6H), 2.73 (s, 2H), 2.18 (s, 8H), 1.95 (s, 2H), 1.68 (s, 2H), 1.38 (s, 2H), 1.24 (s, 4H), 0.92 (s, 6H).

## Example 117

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro furan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 117A

1-(tetrahydrofuran-3-yl)azetidin-3-amine

Tert-butyl azetidin-3-ylcarbamate (0.550 g), dihydrofuran-3(2H)-one (0.412 g) and sodium triacetoxymethylborohydride (1.015 g) were stirred together in dichloromethane (5 mL). After stirring overnight, the reaction was poured into saturated aqueous NaHCO<sub>3</sub> solution (25 mL) and extracted with dichloromethane (50 mL). The organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes gave tert-butyl 1-(tetrahydrofuran-3-yl)azetidin-3-ylcarbamate. The resulting material was treated with HCl/dioxane for 1 hour, and then concentrated to give the title compound.

## Example 117B

3-nitro-4-(1-(tetrahydrofuran-3-yl)azetidin-3-ylamino)benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (0.084 g), 1-(tetrahydrofuran-3-yl)azetidin-3-amine (0.090 g) and triethylamine (0.266 mL) in tetrahydrofuran (3 mL) was heated to 60° C. After stirring for 4 hours, the reaction was cooled, the tetrahydrofuran was removed and the residue was partitioned

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between dichloromethane (200 mL) and water (20 mL). The organic layer was separated, washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated to give the title compound.

## Example 117C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 117B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.39-9.79 (m, 1H), 9.17 (s, 1H), 8.87 (d, 1H), 8.51 (d, 1H), 8.15 (dd, 2H), 7.94 (d, 1H), 7.68 (d, 1H), 7.48-7.42 (m, 1H), 7.23 (d, 2H), 6.91 (d, 2H), 6.69 (d, 1H), 6.54 (dd, 2H), 5.99 (d, 1H), 4.29 (d, 1H), 4.01-3.73 (m, 4H), 3.66 (d, 2H), 3.08 (s, 6H), 2.76 (s, 2H), 2.21 (s, 6H), 2.03-1.83 (m, 3H), 1.64 (s, 2H), 1.42 (d, 2H), 0.93 (s, 6H).

## Example 118

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-((3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 118A

(R)-tert-butyl (1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 118B

(R)-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 118A for EXAMPLE 1A in EXAMPLE 1B.

## Example 118C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-((3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 118B for 1-acetyl piperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.57 (s, 1H), 8.59 (br s, 1H), 8.45 (br s, 1H), 8.02 (d, 1H), 7.95 (m, 1H), 7.71 (m, 1H), 7.56 (d, 1H), 7.45 (m, 1H), 7.35 (m, 3H), 7.05 (m, 2H), 6.90 (br s, 1H), 6.64 (d, 1H), 6.33 (m, 1H), 6.22 (m, 1H), 3.90 (m, 2H), 3.44 (m, 2H), 3.27 (m, 4H), 3.02 (m, 5H), 2.73 (m, 3H), 2.59 (m, 2H), 2.19 (m, 6H), 1.95

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(m, 2H), 1.85 (m, 2H), 1.64 (m, 1H), 1.50 (m, 2H), 1.39 (m, 2H), 1.23 (m, 1H), 0.94 (s, 6H).

## Example 119

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 75F and EXAMPLE 37D in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.39 (s, 1H), 8.08 (d, 1H), 8.04 (d, 1H), 7.41-7.59 (m, 4H), 7.35 (d, 2H), 7.08 (d, 2H), 6.68 (dd, 1H), 6.37-6.43 (m, 1H), 6.20 (s, 1H), 4.38 (d, 2H), 3.73-3.82 (m, 2H), 3.54-3.63 (m, 2H), 3.09 (s, 4H), 2.81 (s, 2H), 2.16-2.39 (m, 5H), 1.94 (s, 2H), 1.79-1.93 (m, 4H), 1.40 (t, 2H), 0.94 (s, 6H).

## Example 120

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

## Example 120A

Trans-4-(aminomethyl)cyclohexanol

Tert-butyl ((1r,4r)-4-hydroxycyclohexyl)methylcarbamate (1 g) in dichloromethane (10 mL) was treated with trifluoroacetic acid (5 mL) at 0° C. for 10 minutes and at room temperature for 30 minutes. The reaction mixture was concentrated and dried in vacuo to provide the title compound as a trifluoroacetic acid salt.

## Example 120B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

A mixture of EXAMPLE 53A (211 mg), EXAMPLE 120A (104 mg) and N-ethyl-N-isopropylpropan-2-amine (0.3 mL) in dimethylsulfoxide (2 mL) was heated at 150° C. in a Biotage Initiator microwave synthesizer for 1.5 hours and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (30 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the title compound. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.61 (t, 1H), 8.53-8.58 (m, 1H), 8.04 (d, 1H), 7.76-7.83 (m, 1H), 7.47-7.56 (m, 3H), 7.34 (d, 2H), 7.07-7.11 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.82-4.99 (m, 1H), 4.50 (d, 1H), 3.26-3.31 (m, 2H), 3.23 (t, 1H), 3.07 (s, 4H), 2.76 (s, 2H), 2.10-2.28 (m, 6H), 2.05 (dd, 1H), 1.95 (s, 2H), 1.84 (t, 2H), 1.52-1.76 (m, 2H), 1.41-1.51 (m, 1H), 1.38 (t, 2H), 0.95-1.25 (m, 4H), 0.92 (s, 6H).

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## Example 121

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

## Example 121A

(4-methoxycyclohexyl)methanol

4-Methoxycyclohexanecarboxylic acid (7 g) in tetrahydrofuran (20 mL) was treated with 1 M (in tetrahydrofuran) borane-tetrahydrofuran complex (100 mL) overnight. The mixture was concentrated and the residue was dissolved in methanol (100 mL) and concentrated HCl (10 mL). The resulting mixture was stirred for 1 hour and concentrated. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the title compound.

## Example 121B

4-((4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with EXAMPLE 121A.

## Example 121C

4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

Separation of the cis and trans mixture of EXAMPLE 121B on a reverse phase HPLC (gradient: 40-55% acetonitrile in 0.1% TFA in water over 25 minutes) provided the title compound.

## Example 121D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 121C in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.39 (s, 1H), 8.34 (s, 1H), 7.96-8.07 (m, 2H), 7.48-7.56 (m, 3H), 7.31-7.42 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.39 (s, 1H), 3.20 (s, 3H), 3.09 (s, 4H), 2.82 (s, 2H), 2.09-2.34 (m, 6H), 1.96 (s, 2H), 1.78-1.86 (m, 3H), 1.54 (dd, 2H), 1.28-1.46 (m, 6H), 0.92 (s, 6H).

## Example 122

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(cyclopropylamino)cyclohexyl]amino)-3-nitrophenylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 122A

Cis-tert-butyl-4-(cyclopropylamino)cyclohexylcarbamate

The title compound was prepared by substituting tert-butyl 4-oxocyclohexylcarbamate for 4'-chlorobiphenyl-2-carbox-

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aldehyde and cyclopropylamine for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 122B

cis-N<sup>1</sup>-cyclopropylcyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 122A for EXAMPLE 39A in EXAMPLE 39B.

## Example 122C

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 122B for EXAMPLE 100B in EXAMPLE 100C. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.28 (d, 1H), 8.59 (d, 1H), 8.44 (d, 1H), 8.37 (dd, 1H), 8.12 (d, 1H), 7.67 (t, 2H), 7.43 (t, 2H), 7.07 (d, 2H), 6.90 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.50 (dd, 1H), 3.56-3.63 (m, 1H), 3.02-3.08 (m, 4H), 2.77 (s, 3H), 2.26 (t, 2H), 2.10-2.16 (m, 4H), 2.06 (ddd, 1H), 1.97 (s, 2H), 1.74-1.82 (m, 2H), 1.61-1.71 (m, 5H), 1.39 (t, 2H), 0.93 (s, 6H), 0.39-0.44 (m, 4H).

## Example 123

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 123A

Trans-tert-butyl-4-(tetrahydro-2H-pyran-4-ylamino)cyclohexylcarbamate

The title compound was prepared by substituting trans-tert-butyl-4-aminocyclohexylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 123B

trans-N1-(tetrahydro-2H-pyran-4-yl)cyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 123A for EXAMPLE 39A in EXAMPLE 39B.

## Example 123C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 123B for EXAMPLE 100B in EXAMPLE 100C.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.28 (d, 1H), 8.48 (d, 1H), 8.38 (dd, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 7.67-7.69 (m, 2H), 7.44 (d, 2H), 7.08 (d, 2H), 6.91 (d, 1H), 6.78 (dd, 1H), 6.59 (d, 1H), 6.48 (dd, 1H), 4.01 (d, 2H), 3.44-3.49 (m, 1H), 3.37-3.43 (m, 2H), 3.01-3.09 (m, 5H), 2.85 (t, 1H), 2.78 (s, 2H), 2.27 (t, 2H), 2.13-2.18 (m, 4H), 2.05 (t, 4H), 1.97 (s, 2H), 1.93 (d, 2H), 1.52-1.60 (m, 2H), 1.44-1.50 (m, 2H), 1.39 (t, 2H), 1.25-1.34 (m, 2H), 0.94 (s, 6H).

## Example 124

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 124A

Trans-4-morpholinocyclohexanol

Trans-4-Aminocyclohexanol (0.5 g), 1-bromo-2-(2-bromoethoxy)ethane (1.07 g) and triethylamine (2.42 mL) were dissolved in anhydrous acetonitrile (20 mL). The reaction mixture was heated at 60° C. overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 7%-10% methanol in dichloromethane to give the title compound.

## Example 124B

Trans-5-bromo-6-(4-morpholinocyclohexyloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 124A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 124C

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 124B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 3.07 (m, 4H), 2.89 (m, 1H), 2.71 (m, 2H), 2.16 (m, 6H), 1.96 (s, 3H), 1.80 (m, 4H), 1.38 (t, 2H), 1.27 (m, 2H), 0.92 (s, 6H).

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## Example 125

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{(4-methoxycyclohexyl)methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 125A

4-(((trans)-4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

Separation of the cis and trans mixture of EXAMPLE 121B on a reverse phase HPLC provided the title compound.

## Example 125B

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{(4-methoxycyclohexyl)methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 125A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.34 (s, 1H), 7.96-8.09 (m, 2H), 7.51 (dd, 3H), 7.32-7.39 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.24 (s, 3H), 3.00-3.15 (m, 5H), 2.83 (s, 2H), 2.09-2.36 (m, 6H), 2.03 (d, 2H), 1.96 (s, 2H), 1.77-1.86 (m, 2H), 1.73 (s, 1H), 1.39 (t, 2H), 1.02-1.17 (m, 4H), 0.92 (s, 6H)

## Example 126

tert-butyl 4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl}-4-fluoropiperidine-1-carboxylate

## Example 126A

tert-butyl 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (5 mL) was treated with 1.0 N LiAlH<sub>4</sub> in THF (2.54 mL) at 0° C. The reaction mixture was stirred at room temperature for 2 hours. Water (0.6 mL) was added to the reaction mixture drop-wise, followed by 2 N aqueous NaOH (0.2 mL). The reaction was stirred for another 1 hour. The solid was removed by filtration via a pack of Celite and washed with ethyl acetate. The filtrate was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 126B

tert-butyl 4-fluoro-4-((2-nitro-4-sulfamoylphenoxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 126A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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## Example 126C

tert-butyl 4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl}-4-fluoropiperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 126B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.36 (s, 2H), 8.02-8.06 (m, 2H), 7.49-7.53 (m, 3H), 7.40 (d, 1H), 7.35 (d, 2H), 7.04 (d, 1H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 3.83-3.85 (m, 2H), 3.09 (s, 4H), 2.33 (s, 2H), 2.27-2.32 (m, 4H), 2.13-2.16 (m, 2H), 1.96 (s, 2H), 1.83-1.92 (m, 2H), 1.67-1.75 (m, 2H), 1.38-1.41 (m, 1H), 0.92 (s, 6H).

## Example 127

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{(4-fluoropiperidin-4-yl)methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 126C for EXAMPLE 1A in EXAMPLE 1B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.14 (d, 1H), 7.90 (d, 2H), 7.80 (dd, 1H), 7.60 (d, 1H), 7.40 (t, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 7.13 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.30 (dd, 1H), 6.26 (d, 1H), 4.28 (d, 2H), 3.10-3.13 (m, 2H), 2.91-3.00 (m, 6H), 2.73 (s, 2H), 1.96-2.02 (m, 4H), 1.77-1.89 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 128

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cyclohexylamino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 128A

tert-butyl 4-(tetrahydro-2H-pyran-4-yl)piperazine-1-carboxylate

The title compound was prepared by substituting tert-butyl piperazine-1-carboxylate for morpholine and dihydro-2H-pyran-4(3H)-one for tert-butyl 4-oxocyclohexylcarbamate in EXAMPLE 39A.

## Example 128B

1-(tetrahydro-2H-pyran-4-yl)piperazine dihydrochloride

To a solution of EXAMPLE 128A (3.92 g) in ether was added HCl (25 mL, 2M in ether) and the reaction mixture was stirred for 16 hours at room temperature. The solid product was filtered off, dried and used in next step without further purification.



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## Example 128C

Trans-tert-butyl-4-(4-(tetrahydro-2H-pyran-4-yl)  
piperazin-1-yl)cyclohexylcarbamate

The title compound was prepared by substituting  
EXAMPLE 128B for morpholine in EXAMPLE 39A.

## Example 128D

trans-4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)  
cyclohexanamine tris(2,2,2-trifluoroacetate)

The title compound was prepared by substituting  
EXAMPLE 128C for EXAMPLE 39A in EXAMPLE 39B.

## Example 128E

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclo-  
hex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-  
{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cy-  
clohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-  
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 128D for EXAMPLE 100B in EXAMPLE 100C.  
<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.28-9.32  
(m, 1H), 8.44 (t, 1H), 8.34-8.39 (m, 2H), 8.10-8.14 (m, 1H),  
7.66-7.69 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (t, 1H),  
6.73-6.77 (m, 1H), 6.52-6.55 (m, 1H), 6.49-6.52 (m, 1H),  
3.99-4.06 (m, 2H), 3.29-3.36 (m, 2H), 3.03-3.09 (m, 4H),  
2.77 (s, 2H), 2.62 (s, 8H), 2.24-2.29 (m, 3H), 2.10-2.16 (m,  
5H), 2.05 (s, 2H), 1.97 (s, 2H), 1.92 (s, 2H), 1.70 (d, 2H), 1.57  
(td, 2H), 1.34-1.43 (m, 4H), 1.20-1.30 (m, 2H), 0.93 (s, 6H).

## Example 129

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-[2-fluoro-  
1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy]-3-  
nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

## Example 129A

(1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methanol

A suspension of piperidin-4-ylmethanol (0.250 g), sodium  
triacetoxymethylborohydride (0.690 g) and 1,3-difluoropropan-2-  
one (0.245 g) were stirred together in dichloromethane. After  
stirring overnight the reaction was poured into saturated  
aqueous NaHCO<sub>3</sub> solution (10 mL) and stirred for 15 min-  
utes. The reaction was extracted with dichloromethane (3×25  
mL), dried over magnesium sulfate, filtered, and concen-  
trated. Silica gel chromatography (GraceResolv 12 g) eluting  
with a gradient of 0.75% to 3% methanol/dichloromethane  
gave the title compound.

## Example 129B

4-((1-(1,3-difluoropropan-2-yl)piperidin-4-yl)meth-  
oxy)-3-nitrobenzenesulfonamide

To a solution of (1-(1,3-difluoropropan-2-yl)piperidin-4-  
yl)methanol (0.068 g) in tetrahydrofuran (1 mL) was added  
sodium hydride (0.056 g) and the reaction stirred for 30  
minutes at room temperature. 4-Fluoro-3-nitrobenzene-

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sulfonamide (0.077 g) was added in one portion and stirring  
was continued for 1 hour. The reaction was poured into water  
(20 mL) and extracted with dichloromethane. The pH of the  
aqueous layer was adjusted to pH~8 and it was extracted with  
dichloromethane (50 mL). The organic layer was dried over  
magnesium sulfate, filtered, and concentrated to give the title  
compound.

## Example 129C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-[2-fluoro-  
1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy]-3-  
nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 129B for EXAMPLE 1F and EXAMPLE 3J for  
EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dim-  
ethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.47-10.98 (m, 1H), 8.33  
(d, 1H), 8.03 (d, 2H), 7.50 (dd, 3H), 7.36 (t, 3H), 7.04 (d, 2H),  
6.67 (d, 1H), 6.39 (dd, 1H), 6.20 (s, 1H), 4.62 (dd, 4H), 4.06  
(d, 2H), 3.18-2.71 (m, 11H), 2.20 (d, 6H), 1.96 (s, 2H), 1.73  
(d, 3H), 1.35 (d, 4H), 0.92 (s, 6H).

## Example 130

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-  
{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]  
amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyri-  
din-5-yloxy)benzamide

## Example 130A

(R)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)pyrroli-  
din-3-ylcarbamate

The title compound was prepared by substituting dihydro-  
2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxalde-  
hyde and (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-bu-  
tyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 130B

(R)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

A solution of EXAMPLE 130A (550 mg) in dichlo-  
romethane (25 mL) was cooled in an ice bath under nitrogen.  
2,2,2-Trifluoroacetic acid (8.333 mL) was added and the reac-  
tion was stirred for 2 hours. The product was obtained by  
concentration and high vacuum drying.

## Example 130C

(R)-3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)pyrroli-  
din-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting  
EXAMPLE 130B for (tetrahydropyran-4-yl)methylamine in  
EXAMPLE 1F.

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## Example 130D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 3J (90 mg), EXAMPLE 130C (64.2 mg), triethylamine (0.077 ml), N,N-dimethylpyridin-4-amine (38.5 mg) in a mixture of dichloromethane (5 ml) and N,N-dimethylformamide (0.5 ml) was added N<sup>1</sup>-(ethylimino)methylene)-N<sup>3</sup>,N<sup>3</sup>-dimethylpropane-1,3-diamine, hydrochloric acid (60.4 mg) and the mixture was stirred 18 hours. This was concentrated on high vacuum and the crude was purified by reverse phase chromatography with ammonium acetate buffer/acetonitrile. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.59 (d, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.65-7.67 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.06 (m, 1H), 3.98 (d, 2H), 3.35 (t, 2H), 3.07 (m, 4H), 2.73-2.80 (m, 4H), 2.68-2.72 (m, 1H), 2.36 (q, 1H), 2.11-2.30 (m, 9H), 1.97 (m, 2H), 1.62-1.71 (m, 3H), 1.48-1.58 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 131

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 131A

tert-butyl (3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 2,2-dimethyldihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 131B

(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 131A for EXAMPLE 130A in EXAMPLE 130B.

## Example 131C

4-((3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 131B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 131D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 131C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (d, 1H), 9.28 (m, 1H), 8.61 (m, 1H), 8.44 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.89 (m, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.07 (m, 4H), 2.71-2.82 (m, 5H), 2.37-2.44 (m, 2H), 2.19-2.29 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.32-1.49 (m, 4H), 1.28 (d, 3H), 1.20 (s, 3H), 0.94 (s, 6H).

## Example 132

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 132A

(S)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 132B

(S)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 132A for EXAMPLE 130A in EXAMPLE 130B.

## Example 132C

(S)-3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 132B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 132D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 132C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.04 (m, 1H), 9.27 (d, 1H), 8.58 (d, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.06 (m, 1H), 3.98 (d, 2H), 3.36 (t, 2H), 3.07 (m, 4H), 2.68-2.80 (m, 5H), 2.36 (m, 1H), 2.09-2.29 (m, 9H), 1.97 (s, 2H), 1.62-1.72 (m, 3H), 1.48-1.60 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

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## Example 133

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 133A

tert-butyl (3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 2,2-dimethyldihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 133B

(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 133A for EXAMPLE 130A in EXAMPLE 130B.

## Example 133C

4-(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)-3-nitro benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 133B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 133D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 133C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (d, 1H), 9.28 (m, 1H), 8.61 (m, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.89 (m, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.07 (m, 4H), 2.71-2.82 (m, 5H), 2.37-2.44 (m, 2H), 2.19-2.29 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.33-1.48 (m, 4H), 1.28 (d, 3H), 1.20 (s, 3H), 0.94 (s, 6H).

## Example 134

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 134A

4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

A solution of EXAMPLE 113A (0.8 g) in dichloromethane (10 mL) and trifluoroacetic acid (10 mL) was stirred at room

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temperature for 2 hours. The solvents were evaporated and the residue triturated with diethyl ether. The resulting solid was dissolved in 5% aqueous sodium carbonate solution (20 mL). The solution was concentrated to dryness and the resulting solid was triturated with a solution of 10% methanol in dichloromethane several times. Evaporation of the organic solvents gave the title compound.

## Example 134B

4-((4-methylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 134A (158 mg) in anhydrous N,N-dimethylformamide (4 mL) was added sodium carbonate (64 mg) and methyl iodide (78 mg). After stirring overnight at room temperature, the mixture was evaporated to dryness. The crude product was then absorbed on silica gel (6 g) and purified on a silica gel column eluting with 10% methanol in dichloromethane to give the title compound.

## Example 134C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 134B for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.92 (m, 1H), 3.86 (d, 1H), 3.67 (dt, 1H), 3.49-3.39 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 3.71 (m, 1H), 2.49 (d, 1H), 2.26 (m, 2H), 2.16 (s, 3H), 2.14 (m, 4H), 2.03 (dt, 1H), 1.97 (s, 2H), 1.90 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 135

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(2-methoxyethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 135A

4-((4-(2-methoxyethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-methoxyethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 135B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(2-methoxyethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 135A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.98 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H),

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7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.93 (m, 1H), 3.87 (d, 1H), 3.70 (dt, 1H), 3.51 (t, 2H), 3.48-3.38 (m, 2H), 3.27 (s, 3H), 3.07 (m, 4H), 2.95 (d, 1H), 2.77 (s, 2H), 2.70 (m, 1H), 2.57 (t, 2H), 2.27-2.07 (m, 8H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 136**

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 136A**

4-((4-acetylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting acetic anhydride for methyl iodide in EXAMPLE 134B.

**Example 136B**

N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 136A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (s, 1H), 8.85 (s, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.10 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (dd, 1H), 6.75 (dd, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.73 (dd, 1H), 3.93-3.65 (m, 2H), 3.60-3.40 (m, 4H), 3.12 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.57 (t, 2H), 2.14 (s, 3H), 2.27-2.07 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 137**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 137A**

ethyl 4-fluorobut-2-enoate

Ethyl 2-fluoroacetate (21.0 g) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at -78° C. was treated dropwise over 45 min with a 1.0 M solution of diisobutylaluminum hydride in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) maintaining the internal temperature below -70° C. Stirring was continued at -78° C. for 30 minutes and then (carbethoxymethylene)triphenylphosphorane (70.0 g) was added in one portion. The reaction mixture was allowed to slowly reach room temperature while stirring overnight. It was then quenched with methanol, filtered and concentrated to give the product as a mixture of isomers (E/Z=3:1).

**Example 137B**

Trans-ethyl

1-benzyl-4-(fluoromethyl)pyrrolidine-3-carboxylate

A mixture of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (4.5 g) and EXAMPLE 137A (2.5 g) in

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dichloromethane (50 mL) was cooled to 0° C., treated dropwise with trifluoroacetic acid (0.15 mL), stirred for 4 hours at 0° C. and neutralized with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was poured into a separatory funnel and the layers separated. The organic layer was washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 0-20% ethyl acetate in hexanes as eluent to give both the cis and trans isomers of the product. Only the trans diastereomers were carried on in the following steps.

**Example 137C**

Trans-ethyl

4-(fluoromethyl)pyrrolidine-3-carboxylate

EXAMPLE 137B (0.83 g) in ethanol (9 mL) was treated with 10% Pd/C (0.208 g) and ammonium formate (1.97 g), refluxed for 1.5 hours, concentrated, dissolved in dichloromethane, filtered through a pad of celite rinsing with dichloromethane, and concentrated to give the product.

**Example 137D**

Trans-1-benzyl 3-ethyl

4-(fluoromethyl)pyrrolidine-1,3-dicarboxylate

EXAMPLE 137C (0.44 g) in dioxane (4 mL) and water (4 mL) at 0° C. was treated sequentially with Na<sub>2</sub>CO<sub>3</sub> (0.89 g) and benzyl chloroformate (0.48 mL). The reaction mixture was stirred at 0° C. for 3 hours and was then allowed to slowly warm to room temperature over 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 10-25% ethyl acetate in hexanes as eluent to give the product.

**Example 137E**

Trans-1-(benzyloxycarbonyl)-4-(fluoromethyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by substituting EXAMPLE 137D for EXAMPLE 15G in EXAMPLE 15H.

**Example 137F**

Trans-benzyl 3-(fluoromethyl)-4-(hydroxymethyl)pyrrolidine-1-carboxylate

EXAMPLE 137E (0.563 g) in tetrahydrofuran (10 mL) at 0° C. was treated dropwise with a 1 M solution of borane in tetrahydrofuran (4 mL), stirred for 3 hours and then slowly quenched with saturated aqueous NH<sub>4</sub>Cl solution. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated to give the product.

**Example 137G**

Trans-benzyl 3-(fluoromethyl)-4-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 137F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.



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## Example 137H

Trans-4-((4-(fluoromethyl)pyrrolidin-3-yl)methoxy)-3-nitrobenzenesulfonamide

EXAMPLE 137G (0.232 g) in acetic acid (2.5 mL) was treated with hydrobromic acid (33 wt % in acetic acid) (0.875 mL) at ambient temperature, stirred for 1 hour and concentrated. The product was free-based using a MEGA BE-SCX column with 1:1 CH<sub>2</sub>Cl<sub>2</sub>/methanol as eluent for the hydrobromic acid and acetic acid. The product was released from the column with 10% (7 M ammonia in methanol) in CH<sub>2</sub>Cl<sub>2</sub> as eluent.

## Example 137I

Trans-4-((4-(fluoromethyl)-1-(oxetan-3-yl)pyrrolidin-3-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 137H for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 137J

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 137I for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.35 (d, 1H), 8.03 (m, 2H), 7.51 (m, 3H), 7.37 (m, 3H), 7.04 (m, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.45 (m, 6H), 4.21 (d, 2H), 3.62 (m, 1H), 3.08 (m, 4H), 2.72 (m, 5H), 2.31 (m, 9H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 138

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 138A

(4-fluorotetrahydro-2H-pyran-4-yl)methyl methanesulfonate

A mixture of EXAMPLE 37C (1.4 g), methanesulfonyl chloride (1.054 mL), triethylamine (2.99 mL), and 4-dimethylaminopyridine (0.051 g) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was stirred at 0° C. for 2 hours, concentrated and chromatographed on silica gel eluting with 30% ethyl acetate in hexanes to give the product.

## Example 138B

2-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)isoin-doline-1,3-dione

A mixture of EXAMPLE 138A (1.8 g) and potassium phthalimide (2.356 g) in N,N-dimethylformamide (30 mL)

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was heated at 150° C. overnight, diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel eluting with 30% ethyl acetate in hexanes to give the product.

## Example 138C

(4-fluorotetrahydro-2H-pyran-4-yl)methanamine

A mixture of EXAMPLE 138B (1.4 g) and hydrazine (1.548 mL) in ethanol (40 mL) was heated at 70° C. overnight, cooled to room temperature, slurried with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and the solid removed by filtration. The filtrate was concentrated and chromatographed on silica gel eluting with 100:5:1 ethyl acetate/methanol/NH<sub>4</sub>OH to give the product.

## Example 138D

4-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (0.44 g), EXAMPLE 138C (0.266 g), and triethylamine (1.11 mL) in tetrahydrofuran (10 mL) was heated at 70° C. overnight, diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel eluting with 50% ethyl acetate in hexanes to give the product.

## Example 138E

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 138D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.62 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.82 (dd, 1H), 7.48-7.54 (m, 3H), 7.34 (d, 2H), 7.24 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.70-3.77 (m, 4H), 3.50-3.55 (m, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.14-2.20 (m, 6H), 1.76-1.84 (m, 4H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 139

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 139A

tert-butyl 4-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)piperidine-1-carboxylate

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetyl piperidin-4-amine with 4-amino-piperidine-1-carboxylic acid tert-butyl ester.

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## Example 139B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylamino)phenylsulfonyl)benzamide

To a cooled (0° C.) solution of EXAMPLE 139A (960 mg) in dichloromethane (10 mL) was added dropwise trifluoroacetic acid (5 mL). The mixture was stirred at the temperature for 3 hours. Then, the mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (200 mL) and washed with aqueous NaHCO<sub>3</sub> and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered, and evaporation of the solvent from the filtrate gave the title compound.

## Example 139C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 139B (120 mg) in tetrahydrofuran (3 mL) and acetic acid (1 mL) was added oxetan-3-one (50.8 mg) and MP-cyanoborohydride (2.15 mmol/g, 150 mg). The mixture was stirred at room temperature overnight. The mixture was filtered. The filtrate was concentrated and the residue was loaded on a silica gel cartridge and eluted with 5-10% 7N NH<sub>3</sub> in methanol in dichloromethane to give the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.62 (s, 1H), 8.51 (d, 1H), 8.20 (d, 1H), 7.99 (d, 1H), 7.74 (m, 1H), 7.48 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.36 (dd, 1H), 6.20 (d, 1H), 4.54 (t, 2H), 4.43 (t, 2H), 3.66 (m, 1H), 3.44 (m, 3H), 3.04 (m, 5H), 2.73 (s, 2H), 2.61 (m, 2H), 2.12 (m, 11H), 1.61 (m, 2H), 1.38 (t, 2H), 0.93 (m, 6H).

## Example 140

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-[(1-cyclobutyl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with cyclobutanone. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.47 (d, 1H), 8.12 (d, 1H), 7.97 (d, 1H), 7.74 (d, 1H), 7.53 (d, 1H), 7.45 (m, 1H), 7.36 (m, 3H), 7.02 (m, 3H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.22 (d, 1H), 3.74 (m, 1H), 2.97 (m, 6H), 2.73 (s, 3H), 2.15 (m, 15H), 1.67 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

## Example 141

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with 2,2-dimethyltetrahydropyran-4-one. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.50 (d, 1H), 8.15 (m, 1H), 7.99 (d, 1H), 7.78 (m, 1H), 7.62 (m, 1H), 7.47 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.65 (m, 2H), 6.35 (dd, 1H), 6.21 (d, 1H),

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4.56 (d, 3H), 3.89 (m, 3H), 3.67 (m, 6H), 3.45 (m, 2H), 3.04 (m, 3H), 2.75 (m, 3H), 2.14 (m, 3H), 1.71 (m, 5H), 1.16 (s, 9H).

## Example 142

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([[(3S)-1-cyclopropylpyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 142A

(S)-tert-butyl 1-cyclopropylpyrrolidin-3-ylcarbamate

(S)-tert-butyl pyrrolidin-3-ylcarbamate (415 mg), (1-ethoxycyclopropoxy)trimethylsilane (1.8 mL) and molecular sieves (500 mg) were combined in methanol (4.5 mL). Acetic acid (1.3 mL) was added, followed by sodium cyanoborohydride (420 mg). The resulting mixture was heated to reflux for 4 hours. Insoluble material was filtered off and reaction was made basic to pH 14 with addition of 6M aqueous NaOH solution. The solution was extracted three times with diethyl ether, and the combined extracts were dried over MgSO<sub>4</sub>, filtered and concentrated to obtain an oil, which was purified by flash chromatography, eluting first with 100% dichloromethane, followed by 5% methanol/dichloromethane and 10% methanol/dichloromethane.

## Example 142B

(S)-1-cyclopropylpyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 142A for EXAMPLE 1A in EXAMPLE 1B.

## Example 142C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([[(3S)-1-cyclopropylpyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 142B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.51 (m, 2H), 8.30 (m, 1H), 8.00 (br s, 1H), 7.77 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.97 (br s, 1H), 6.67 (dd, 1H), 6.36 (m, 1H), 6.21 (m, 1H), 4.19 (m, 1H), 3.00 (m, 5H), 2.74 (m, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.15 (m, 6H), 1.95 (s, 2H), 1.78 (br s, 1H), 1.68 (m, 1H), 1.38 (t, 2H), 1.23 (m, 1H), 0.92 (s, 6H), 0.39 (m, 4H).

## Example 143

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(1-tetrahydro furan-3-yl)piperidin-4-yl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with 3-oxotetrahydrofuran. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.53 (d, 1H), 8.21 (m, 1H), 8.02 (m, 1H), 7.80

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(dd, 1H), 7.49 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.67 (dd, 1H), 6.37 (m, 1H), 6.19 (d, 1H), 4.29 (m, 3H), 3.73 (m, 6H), 3.09 (m, 4H), 2.76 (m, 2H), 2.05 (m, 8H), 1.68 (m, 2H), 1.37 (m, 2H), 0.94 (s, 6H).

**Example 144**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 144A**

(R)-tert-butyl 1-cyclopropylpyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for (S)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 142A.

**Example 144B**

(R)-1-cyclopropylpyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 144A for EXAMPLE 1A in EXAMPLE 1B.

**Example 144C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 144B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.53 (d, 2H), 8.32 (d, 1H), 8.02 (d, 1H), 7.81 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.37 (m, 1H), 6.20 (d, 1H), 4.21 (m, 1H), 3.00 (m, 5H), 2.74 (m, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.15 (m, 6H), 1.95 (s, 2H), 1.74 (br s, 1H), 1.66 (m, 1H), 1.38 (t, 2H), 1.23 (m, 1H), 0.92 (s, 6H), 0.39 (m, 4H).

**Example 145**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[(3S)-1-tetrahydro-2H-pyran-4-yl]pyrrolidin-3-yl)methyl}amino]phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 145A**

(S)-tert-butyl (1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

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zine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

**Example 145B**

(S)-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 145A for EXAMPLE 1A in EXAMPLE 1B.

**Example 145C**

(S)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-((1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 145B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.61 (br s, 1H), 8.46 (s, 1H), 7.96 (d, 1H), 7.72 (m, 1H), 7.54 (d, 1H), 7.45 (t, 1H), 7.37 (br s, 2H), 7.34 (d, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.22 (d, 1H), 3.89 (m, 2H), 3.38 (m, 4H), 3.27 (m, 4H), 3.02 (m, 5H), 2.73 (s, 2H), 2.61 (m, 1H), 2.18 (m, 6H), 2.05 (m, 1H), 1.95 (m, 2H), 1.85 (m, 2H), 1.64 (m, 1H), 1.50 (m, 2H), 1.38 (m, 2H), 0.94 (s, 6H).

**Example 146**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using 3-amino-2,2-dimethylpropan-1-ol in place of EXAMPLE 120A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.35 (s, 1H), 8.96 (t, 1H), 8.56 (d, 1H), 8.05 (d, 1H), 7.79 (dd, 1H), 7.46-7.56 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 5.10 (t, 1H), 3.29 (d, 1H), 3.24 (d, 1H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (d, 12H).

**Example 147**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 147A**

tert-butyl (1-(methylsulfonyl)piperidin-3-yl)methylcarbamate

tert-Butyl piperidin-3-ylmethylcarbamate (500 mg) was dissolved in anhydrous dichloromethane (10 mL), and methanesulfonyl chloride (0.181 mL) was added followed by the addition of triethylamine (1.3 mL). The reaction mixture was stirred at room temperature overnight. The organic solvent was removed under vacuum. The residue was purified with

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flash column chromatography on silica gel eluting with 0-70% ethyl acetate in hexane to give the title compound.

## Example 147B

(1-(methylsulfonyl)piperidin-3-yl)methanamine

EXAMPLE 147A (400 mg) was suspended in 4N HCl in dioxane (10 mL) followed by the addition of anhydrous methanol (1 mL). The clear solution was stirred at room temperature for 2 hours. The organic solvent was removed under vacuum. The solid residue was used in the next step without further purification.

## Example 147C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-(methylsulfonyl)piperidin-3-yl)methyl]amino}-3-nitrophenylsulfonyle-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 53A (50 mg), EXAMPLE 147B (26 mg) and triethylamine (0.088 mL) were dissolved in anhydrous dioxane (1 mL) and N,N-dimethylformamide (0.2 mL). The reaction vial was heated in a Biotage Initiator microwave reactor at 130° C. for 25 minutes. The solvent was removed under vacuum. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 20-80% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.52 (m, 1H), 3.40 (m, 2H), 3.06 (m, 4H), 2.84 (s, 3H), 2.75 (m, 2H), 2.75 (m, 4H), 2.58 (m, 1H), 2.16 (m, 6H), 1.95 (s, 3H), 1.76 (m, 2H), 1.52 (m, 1H), 1.37 (m, 2H), 0.92 (s, 6H).

## Example 148

N-[(4-{[(1-acetyl)piperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 148A

tert-butyl (1-acetyl)piperidin-3-yl)methylcarbamate

The title compound was prepared by substituting acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

## Example 148B

1-(3-(aminomethyl)piperidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 148A for EXAMPLE 147A in EXAMPLE 147B.

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Example 148C

N-[(4-{[(1-acetyl)piperidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 148B for EXAMPLE 147B in EXAMPLE 147C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 3.07 (m, 4H), 2.89 (m, 1H), 2.71 (m, 2H), 2.16 (m, 6H), 1.96 (s, 3H), 1.80 (m, 4H), 1.38 (t, 2H), 1.27 (m, 2H), 0.92 (s, 6H).

## Example 149

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 149A

(R)-tert-butyl

1-(methylsulfonyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate in EXAMPLE 147A.

## Example 149B

(R)-1-(methylsulfonyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 149A for EXAMPLE 147A in EXAMPLE 147B.

## Example 149C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 149B for EXAMPLE 147B in EXAMPLE 147C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 8.02 (d, 1H), 7.86 (dd, 1H), 7.49 (m, 3H), 7.33 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.41 (m, 1H), 3.69 (m, 1H), 3.39 (m, 3H), 3.06 (m, 4H), 2.97 (s, 3H), 2.76 (m, 2H), 2.27 (m, 8H), 1.93 (m, 2H), 1.54 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).



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## Example 150

4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 150A

## Ethyl

2-hydroxy-3,3-dimethylcyclohex-1-enecarboxylate

Into a 500 mL round-bottomed flask was added diisopropylamine (3.5 mL) in ether (200 mL). After cooling to  $-30^{\circ}\text{C}$ ., butyllithium (16 mL) (1.6M in hexane) was added slowly. After stirring 30 minutes, the temperature was cooled to  $-5^{\circ}\text{C}$ .. 2,2-Dimethylcyclohexanone (3 g) was added slowly. The mixture was warmed up to  $0^{\circ}\text{C}$ . and stirred for 1 hour. After cooling to  $-5^{\circ}\text{C}$ ., hexamethylphosphoramide (8 mL) and ethyl carbonocyanide (2.5 mL) were added. After stirring at  $-5^{\circ}\text{C}$ . for 20 minutes, and warming to room temperature, the reaction was stirred for 1 hour. The mixture was poured into cold water, and the layers were separated. The aqueous layer was extracted with ether (3x20 mL). The combined organic layers were washed with saturated aqueous  $\text{NH}_4\text{Cl}$  (3x20 mL). After drying over  $\text{Na}_2\text{SO}_4$ , the mixture was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography on silica with 0-10% ethyl acetate in hexanes to provide the title compound.

## Example 150B

Ethyl 3,3-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 150A for EXAMPLE 101A in EXAMPLE 101B.

## Example 150C

Ethyl 2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 150B for EXAMPLE 101B in EXAMPLE 101C.

## Example 150D

(2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methanol

In a 200 mL round-bottomed flask was added EXAMPLE 150C (0.97 g) and lithium borohydride (0.47 g) in ether (20 mL) to give a suspension. Methanol (2.2 mL) was added slowly. The mixture was refluxed overnight. The reaction was then cooled, and methanol was added to quench the reaction. 1N aqueous HCl was then added until the  $\text{pH} < 7$ , and ether (3x30 mL) was used to extract the product. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concen-

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trated. The crude material was purified by flash chromatography on silica with 0-25% ethyl acetate in hexanes to provide the title compound.

## Example 150E

2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enecarbaldehyde

Into a 100 mL round-bottomed flask was added EXAMPLE 150D (0.3 g) and Dess-Martin Periodinane (0.6 g) in dichloromethane (10 mL) to give a suspension. The mixture was stirred at room temperature overnight. After filtration, the mixture was washed with saturated aqueous  $\text{NaHCO}_3$  (2x20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by flash chromatography on silica with 0-25% ethyl acetate in hexanes to provide the title compound.

## Example 150F

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 150E for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 150G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 150F for EXAMPLE 101E in EXAMPLE 101F.

## Example 150H

4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 150G for EXAMPLE 3J and EXAMPLE 1F for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, dimethyl sulfoxide- $d_6$ )  $\delta$  11.50 (s, 1H), 8.36 (m, 1H), 8.32 (m, 1H), 7.91 (d, 1H), 7.59 (m, 2H), 7.40 (t, 1H), 7.35 (d, 2H), 7.25 (m, 1H), 6.94 (d, 2H), 6.79 (d, 1H), 6.60 (m, 1H), 6.29 (m, 1H), 6.24 (d, 1H), 3.83 (m, 2H), 3.25 (m, 4H), 2.98 (m, 4H), 2.42 (s, 2H), 2.14 (m, 6H), 1.60 (m, 6H), 1.25 (m, 3H), 0.86 (s, 6H).

## Example 151

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 151A

1-(1,3-difluoropropan-2-yl)azetidin-3-amine

To a solution of tert-butyl azetidin-3-ylcarbamate (0.256 g) and 1,3-difluoropropan-2-one (0.154 g) in dichloromethane

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(2 mL) was added sodium triacetoxymethylborohydride (0.473 g) and the reaction was allowed to stirred at room temperature. After 16 hours, the reaction was quenched with saturated NaHCO<sub>3</sub> solution (10 mL) and extracted into dichloromethane (25 mL). The organic layer was dried and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.5% to 3.5% methanol/dichloromethane followed by treatment with HCl (4.0M in dioxane, 3 mL) and methanol (0.5 mL) for 2 hours gave the title compound after concentration.

**Example 151B**

4-(1-(1,3-difluoropropan-2-yl)azetidin-3-ylamino)-3-nitrobenzenesulfonamide

To a suspension of 4-chloro-3-nitrobenzenesulfonamide (0.225 g) and 1-(1,3-difluoropropan-2-yl)azetidin-3-amine (0.193 g) in dioxane (5 mL) was added diisopropylamine (0.832 mL). The reaction was sonicated and then heated to 100° C. After stirring overnight, the reaction was concentrated and loaded onto silica gel (GraceResolv 12 g) and eluted with a gradient of 0.5% to 3.5% methanol/dichloromethane to give the title compound.

**Example 151C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-(2-fluoro-1-(fluoromethyl)ethyl)azetidin-3-yl)amino]-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 151B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.54-11.28 (m, 1H), 8.54 (d, 1H), 8.45 (s, 1H), 8.01 (d, 1H), 7.82 (d, 1H), 7.48 (d, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 (d, 1H), 6.67 (d, 1H), 6.37 (s, 1H), 6.20 (s, 1H), 4.64-4.23 (m, 6H), 3.81 (s, 2H), 3.08 (s, 4H), 2.75 (s, 3H), 2.15 (s, 7H), 1.95 (s, 2H), 1.38 (s, 2H), 0.92 (s, 6H).

**Example 152**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-(methylsulfonyl)pyrrolidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 152A**

tert-butyl  
(1-(methylsulfonyl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate in EXAMPLE 147A.

**Example 152B**

(1-(methylsulfonyl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 152A for EXAMPLE 147A in EXAMPLE 147B.

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-(methylsulfonyl)pyrrolidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 152B for EXAMPLE 147B in EXAMPLE 147C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.49 (m, 2H), 7.99 (s, 1H), 7.73 (m, 1H), 7.53 (d, 1H), 7.47 (s, 1H), 7.42 (m, 1H), 7.34 (d, 2H), 7.04 (m, 3H), 6.65 (m, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 3.41 (m, 4H), 3.22 (m, 2H), 3.03 (m, 4H), 2.89 (s, 3H), 2.73 (m, 2H), 2.59 (m, 1H), 2.17 (m, 6H), 2.00 (m, 4H), 1.68 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

**Example 153**

N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 153A**

tert-butyl (1-acetylpyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate and acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

**Example 153B**

1-(3-(aminomethyl)pyrrolidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 153A for EXAMPLE 147A in EXAMPLE 147B.

**Example 153C**

N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 153B for EXAMPLE 147B in EXAMPLE 147C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.62 (m, 1H), 8.54 (s, 1H), 8.03 (m, 1H), 7.78 (d, 1H), 7.50 (m, 3H), 7.35 (t, 2H), 7.09 (s, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.20 (s, 1H), 3.56 (m, 1H), 3.42 (m, 4H), 3.43 (m, 4H), 3.23 (m, 1H), 3.07 (m, 4H), 2.74 (m, 2H), 2.16 (m, 6H), 1.93 (m, 5H), 1.38 (t, 2H), 0.93 (s, 6H).

**Example 154**

N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 154A**

(R)-tert-butyl 1-acetylpyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperidin-3-yl-

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methylcarbamate and acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

**Example 154B**

(R)-1-(3-aminopyrrolidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 154A for EXAMPLE 147A in EXAMPLE 147B.

**Example 154C**

N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 154B for EXAMPLE 147B in EXAMPLE 147. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (s, 1H), 8.50 (s, 1H), 8.17 (d, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.10 (m, 1H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 4.34 (m, 1H), 3.81 (m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 3.05 (m, 4H), 2.74 (s, 2H), 2.19 (m, 9H), 1.96 (m, 5H), 1.38 (t, 2H), 0.94 (s, 6H).

**Example 155**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using 3-methoxy-2,2-dimethylpropan-1-amine in place of EXAMPLE 120A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.32 (s, 1H), 8.92 (t, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.46-7.55 (m, 3H), 7.34 (d, 2H), 7.08 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.36-6.42 (m, 1H), 6.19 (d, 1H), 3.25-3.30 (m, 5H), 3.19 (s, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.96 (s, 6H), 0.92 (s, 6H).

**Example 156**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 156A**

4-(((1R,3R)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1R,3R)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 156B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 156A for EXAMPLE 130C in EXAMPLE

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130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.29 (s, 1H), 8.62 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.85 (d, 1H), 6.74 (dd, 1H), 6.54 (s, 1H), 6.49 (m, 1H), 4.60 (m, 1H), 3.19 (dd, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (t, 2H), 2.20-2.07 (m, 6H), 2.00 (m, 1H), 1.97 (s, 2H), 1.90 (m, 1H), 1.56 (m, 1H), 1.39 (t, 2H), 1.34 (m, 1H), 0.93 (s, 6H).

**Example 157**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 157A**

4-(((1S,3S)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1S,3S)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 157B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 157A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.29 (s, 1H), 8.60 (t, 1H), 8.44 (d, 1H), 8.32 (dd, 1H), 8.14 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.55 (s, 1H), 6.49 (m, 1H), 4.60 (m, 1H), 3.19 (dd, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (t, 2H), 2.20-2.07 (m, 6H), 2.00 (m, 1H), 1.97 (s, 2H), 1.90 (m, 1H), 1.56 (m, 1H), 1.39 (t, 2H), 1.34 (m, 1H), 0.93 (s, 6H).

**Example 158**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 158A**

4-(((1S,3R)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1S,3R)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 158B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 158A for EXAMPLE 130C in EXAMPLE

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130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.94 (s, 1H), 9.25 (d, 1H), 8.59 (t, 1H), 8.48 (d, 1H), 8.27 (m, 2H), 7.66 (m, 2H), 7.45 (d, 2H), 7.08 (d, 2H), 6.77 (dd, 1H), 6.72 (d, 1H), 6.60 (d, 1H), 6.47 (m, 1H), 4.53 (m, 1H), 3.30 (m, 2H), 3.06 (m, 4H), 2.78 (s, 2H), 2.27 (m, 3H), 2.19-2.10 (m, 5H), 1.98 (m, 3H), 1.85-1.66 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 159**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 159A**

4-(((1R,3S)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1R,3S)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 159B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 158A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (s, 1H), 9.28 (d, 1H), 8.59 (t, 1H), 8.44 (d, 1H), 8.29 (d, 1H), 8.13 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.08 (d, 2H), 6.82 (dd, 1H), 6.74 (d, 1H), 6.55 (d, 1H), 6.48 (m, 1H), 4.53 (m, 1H), 3.34 (m, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.27 (m, 3H), 2.19-2.10 (m, 5H), 1.97 (m, 3H), 1.85-1.66 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 160**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1S)-2-oxopiperidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (S)-3-aminopiperidin-2-one for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (br s, 1H), 8.88 (d, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.95 (br s, 1H), 7.83 (dd, 1H), 7.55-7.46 (m, 3H), 7.35 (d, 2H), 7.16 (d, 1H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.21 (d, 1H), 4.41 (m, 1H), 3.22 (m, 2H), 3.09 (br s, 4H), 2.78 (br s, 2H), 2.35-2.09 (m, 8H), 1.96 (br s, 2H), 1.86 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-({[1-(2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 161A**

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)azetidine-1-carboxylate

EXAMPLE 82 (305 mg), tert-butyl 3-(aminomethyl)azetidine-1-carboxylate (86 mg) and diisopropyl amine (0.202 mL) in dioxane (3 mL) were heated to 110° C. After stirring overnight, the reaction was concentrated. Silica gel chromatography (Reveleris, 12 g) eluting with a gradient of 0.5% to 3% methanol/dichloromethane (Flow=36 ml/minute) gave the title compound.

**Example 161B**

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(azetidin-3-ylmethylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

To a solution of EXAMPLE 161A (0.257 g) in dichloromethane (5 mL) was added trifluoroacetic acid (0.211 mL). After 30 minutes an additional 0.2 mL of trifluoroacetic acid was added. After 3 hours, the reaction was concentrated to give the title compound.

**Example 161C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-({[1-(2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A solution of EXAMPLE 161B (0.118 g), sodium triacetoxyborohydride (0.035 g) and 1,3-difluoropropan-2-one (0.012 g) were stirred together in dichloromethane (1 mL) overnight. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> solution (10 mL) and extracted into dichloromethane (30 mL). The organic layer was dried and concentrated. Silica gel chromatography (Reveleris 12 g) eluting with a gradient of 0.5% to 3.5% methanol/dichloromethane over 30 minutes (Flow=36 ml/min) gave the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.47-11.21 (m, 1H), 8.85 (s, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.80 (dd, 1H), 7.54-7.45 (m, 3H), 7.33 (s, 2H), 7.04 (d, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.43 (dt, 4H), 3.56 (t, 2H), 3.46 (s, 2H), 3.12 (m, 6H), 2.74 (m, 3H), 2.17 (m, 7H), 1.95 (s, 2H), 1.39 (d, 2H), 0.92 (s, 6H).

**Example 162**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-oxetan-3-ylazetidin-3-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 161C. <sup>1</sup>H



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NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.66 (s, 1H), 11.51-11.03 (m, 1H), 8.81 (s, 1H), 8.54 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.50 (dd, 3H), 7.34 (d, 2H), 7.04 (d, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.57 (s, 2H), 4.43-4.35 (m, 2H), 3.82 (s, 1H), 3.59 (t, 2H), 3.44 (t, 2H), 3.20 (s, 2H), 3.06 (s, 4H), 2.73 (s, 3H), 2.18 (s, 6H), 1.95 (s, 2H), 1.39 (d, 2H), 0.92 (s, 6H).

## Example 163

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-yl)piperidin-4-yl]methyl}amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 163A

tert-butyl 4-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 4-(aminomethyl)piperidine-1-carboxylate for 1-acetylpiperidin-4-amine in EXAMPLE 53B.

## Example 163B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylmethylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 163A for EXAMPLE 1A in EXAMPLE 1B.

## Example 163C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-yl)piperidin-4-yl]methyl}amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 163B for EXAMPLE 161B and oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 161C.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.68 (s, 1H), 8.60 (t, 1H), 8.54 (d, 1H), 8.03 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.09 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.55 (t, 2H), 4.46 (t, 2H), 3.52 (br s, 1H), 3.28 (m, 2H), 3.17 (d, 1H), 3.06 (m, 4H), 2.82 (m, 2H), 2.74 (m, 2H), 2.17 (m, 6H), 1.95 (m, 3H), 1.72 (m, 3H), 1.38 (t, 2H), 1.28 (m, 2H), 0.92 (s, 6H).

## Example 164

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropyl)piperidin-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 163B for (S)-tert-butyl pyrrolidin-3-ylcarbamate

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in EXAMPLE 142A.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.96 (br s, 1H), 11.62 (br s, 1H), 8.50 (m, 2H), 7.98 (d, 1H), 7.72 (m, 1H), 7.52 (d, 1H), 7.45 (m, 2H), 7.34 (d, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.22 (d, 1H), 3.28 (m, 3H), 3.04 (m, 5H), 2.72 (s, 2H), 2.64 (m, 1H), 2.64 (m, 1H), 2.36 (m, 1H), 2.16 (m, 7H), 1.95 (s, 2H), 1.68 (m, 3H), 1.38 (t, 2H), 1.18 (m, 3H), 0.94 (s, 6H), 0.35 (m, 3H).

## Example 165

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 165A

4-((4-(2-fluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-fluoroethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 165B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 165A for EXAMPLE 130C in EXAMPLE 130D.  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 3.93 (m, 1H), 4.63, 4.51 (dt, 2H), 3.95-3.85 (m, 2H), 3.68 (dt, 1H), 3.43-3.37 (m, 2H), 3.07 (m, 4H), 2.92 (d, 1H), 2.77 (s, 2H), 2.65 (m, 2H), 2.59 (m, 1H), 2.26 (m, 2H), 2.17-2.08 (m, 5H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 166

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 166A

4-((4-(2,2-difluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2,2-difluoroethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 166B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 166A for EXAMPLE 130C in EXAMPLE

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130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.93 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 6.31, 6.20, 6.09 (tt, 1H), 3.90 (m, 1H), 3.85 (d, 1H), 3.67 (dt, 1H), 3.49-3.30 (m, 2H), 3.07 (m, 4H), 2.84 (d, 1H), 2.82-2.75 (m, 4H), 2.69 (d, 1H), 2.33 (dt, 1H), 2.27-2.20 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 167

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 167A

4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 173A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 167B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 167A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.39 (s, 1H), 8.09 (d, 1H), 8.04 (d, 1H), 7.52 (m, 4H), 7.35 (d, 2H), 7.05 (m, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.57 (t, 2H), 4.48 (m, 2H), 4.38 (d, 2H), 4.02 (m, 1H), 3.63 (m, 2H), 3.08 (m, 4H), 2.74 (m, 4H), 2.17 (m, 6H), 1.88 (m, 6H), 1.40 (t, 2H), 0.93 (s, 6H).

## Example 168

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-yl]pyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 168A

(S)-methyl 4,4-difluoropyrrolidine-2-carboxylate

(S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate (0.472 g) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was treated with

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trifluoroacetic acid (1.4 mL), stirred at ambient temperature for 4 hours, and concentrated. The product was free-based using a MEGA BE-SCX column with 1:1 CH<sub>2</sub>Cl<sub>2</sub>/methanol as eluent for the trifluoroacetic acid. The product was released from the column with 5% (7 M ammonia in methanol) in CH<sub>2</sub>Cl<sub>2</sub> as eluent.

## Example 168B

(S)-methyl 4,4-difluoro-1-(oxetan-3-yl)pyrrolidine-2-carboxylate

The title compound was prepared by substituting EXAMPLE 168A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 168C

(S)-(4,4-difluoro-1-(oxetan-3-yl)pyrrolidin-2-yl)methanol

EXAMPLE 168B (0.180 g) in tetrahydrofuran (3 mL) was treated sequentially with a solution of calcium chloride (0.245 g) in ethanol (3 mL) and NaBH<sub>4</sub> (0.167 g) and then stirred at ambient temperature for 7 hours. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl solution and extracted with ethyl acetate. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 50% ethyl acetate in hexanes as eluent to give the product.

## Example 168D

(S)-4-((4,4-difluoro-1-(oxetan-3-yl)pyrrolidin-2-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 168C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 168E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-yl]pyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 168D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.38 (s, 1H), 8.06 (m, 2H), 7.49 (m, 4H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.21 (s, 1H), 4.54 (m, 3H), 4.43 (t, 1H), 4.23 (m, 1H), 4.12 (m, 2H), 3.44 (m, 2H), 3.12 (m, 7H), 2.58 (m, 1H), 2.29 (m, 7H), 1.97 (s, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

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Example 169

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 169A

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpipeidin-4-amine with tert-butyl 3-(aminomethyl)morpholine-4-carboxylate.

Example 169B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-(morpholin-3-ylmethylamino)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 139B by replacing EXAMPLE 139A with EXAMPLE 169A.

Example 169C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and tetrahydropyran-4-one, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.77 (m, 1H), 8.57 (d, 1H), 8.05 (d, 1H), 7.84 (dd, 1H), 7.52 (m, 3H), 7.34 (m, 2H), 7.03 (m, 3H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.18 (d, 1H), 3.86 (m, 2H), 3.72 (m, 2H), 3.11 (m, 6H), 2.74 (m, 4H), 2.20 (m, 6H), 1.95 (m, 3H), 1.51 (m, 7H), 0.92 (s, 6H).

Example 170

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclobutylmorpholin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and cyclobutanone. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.72 (s, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.84 (dd, 1H), 7.52 (m, 3H), 7.34 (m, 3H), 7.03 (m, 4H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.18 (d, 1H), 3.47 (m, 3H), 3.10 (m, 6H), 2.72 (m, 6H), 2.25 (m, 8H), 1.95 (m, 4H), 1.56 (m, 3H), 1.38 (m, 2H), 0.92 (s, 6H).

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Example 171

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydrofuran-3-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and 3-oxotetrahydrofuran, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.66 (s, 1H), 8.53 (d, 1H), 8.01 (d, 1H), 7.80 (d, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.98 (d, 1H), 6.66 (dd, 1H), 6.37 (d, 1H), 6.19 (d, 1H), 3.68 (m, 8H), 3.05 (m, 6H), 2.85 (m, 3H), 2.73 (s, 2H), 2.25 (m, 6H), 1.91 (m, 3H), 1.37 (m, 3H), 0.95 (m, 6H).

Example 172

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 163B for tert-butyl piperazine-1-carboxylate and 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.40 (br s, 1H), 8.57 (m, 2H), 8.03 (d, 1H), 7.78 (d, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 4.63 (d, 2H), 4.53 (d, 2H), 3.28 (m, 2H), 3.07 (m, 4H), 2.89 (m, 2H), 2.74 (m, 2H), 2.40 (m, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.67 (m, 3H), 1.38 (t, 2H), 1.23 (m, 3H), 0.94 (s, 6H).

Example 173

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 173A

4-((4-fluoropiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 126B for EXAMPLE 1A in EXAMPLE 1B.

Example 173B

4-((1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

To EXAMPLE 173A (0.24 g) in methanol (3 mL) was added 3 Å molecular sieves (0.1 g), followed sequentially by acetic acid (0.31 mL), (1-ethoxycyclopropoxy)trimethylsilane (0.64 mL), and sodium cyanoborohydride (0.148 g). The reaction was heated under reflux overnight. After cooling, the reaction mixture was loaded onto a silica gel column. After drying, the column was eluted with 100:20:2 ethyl acetate/methanol/NH<sub>4</sub>OH to give the title compound.

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## Example 173C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 173B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.33 (s, 1H), 8.01 (m, 2H), 7.53 (d, 1H), 7.48-7.49 (m, 2H), 7.34-7.38 (m, 3H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.32 (d, 2H), 3.70-3.77 (m, 2H), 3.07 (s, 4H), 2.92 (s, 2H), 2.80 (s, 2H), 2.58 (s, 2H), 2.25 (s, 4H), 2.13-2.16 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H), 0.40-0.49 (m, 4H).

## Example 174

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A suspension of EXAMPLE 53A (120 mg), (4-methoxyphenyl)methanamine (31 mg) and Hunig's Base (0.159 mL) in dimethylsulfoxide (2 mL) was heated for 2 hours at 150° C. in a Biotage Initiator microwave reactor. The reaction mixture was diluted with methanol (2 mL) and purified by reverse phase HPLC (C8, 30%-100% CH<sub>3</sub>CN/water/0.1% trifluoroacetic acid). <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.32 (d, 1H), 9.17 (t, 1H), 8.43 (d, 1H), 8.28 (dd, 1H), 8.08 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.38 (d, 2H), 7.07 (d, 2H), 6.97-7.02 (m, 2H), 6.90 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.55 (d, 2H), 3.68 (s, 3H), 3.03-3.09 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10-2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 175

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-trifluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.38 (t, 1H), 9.31 (d, 1H), 8.42 (d, 1H), 8.28 (dd, 1H), 8.08 (d, 1H), 7.65 (ddd, 2H), 7.41-7.46 (m, 3H), 7.36-7.40 (m, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (d, 1H), 4.73 (d, 2H), 3.02-3.08 (m, 4H), 2.77 (s, 2H), 2.22-2.28 (m, 2H), 2.09-2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 176

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-methoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.27-9.32 (m, 2H), 8.42 (d, 1H), 8.26 (dd, 1H), 8.08 (d, 1H), 7.64-7.67 (m, 2H), 7.44 (d, 2H), 7.32 (t,

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1H), 7.14 (s, 1H), 7.04-7.09 (m, 3H), 6.88-6.94 (m, 2H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.48-6.50 (m, 1H), 4.64 (d, 2H), 3.68 (s, 3H), 3.03-3.09 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10-2.18 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 177

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (4-difluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.32 (d, 1H), 9.28 (t, 1H), 8.42 (d, 1H), 8.28 (dd, 1H), 8.07 (d, 1H), 7.66 (t, 1H), 7.64 (d, 1H), 7.58 (s, 1H), 7.44 (s, 2H), 7.26 (s, 1H), 7.25 (d, 1H), 7.07 (d, 2H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.64 (d, 2H), 3.03-3.10 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.11-2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 178

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 1,4-dioxaspiro[4.5]dec-8-ylamine for 1-acetyl piperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (br s, 1H), 8.55 (d, 1H), 8.26 (d, 1H), 8.04 (d, 1H), 7.81 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 3.89 (s, 4H), 3.78 (m, 1H), 3.07 (br s, 4H), 2.78 (br s, 2H), 2.28-2.11 (m, 6H), 2.00-1.88 (m, 4H), 1.75-1.57 (m, 4H), 1.54-1.35 (m, 4H), 0.92 (s, 6H).

## Example 179

Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 179A

tert-butyl trans-4-acetamidocyclohexylcarbamate

Tert-butyl (trans)-4-aminocyclohexylcarbamate (1.500 g) and triethylamine (2.93 mL, 2.125 g) were added to dichloromethane and stirred until the tert-butyl (trans)-4-aminocyclohexylcarbamate had dissolved completely. Acetyl chloride (0.577 g) was added slowly, and the solution was stirred at room temperature for 16 hours. The solvent was removed, and the residue taken up in ethyl acetate, washed with pH 4 buffer, washed with brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum.

## Example 179B

N-(trans-4-aminocyclohexyl)acetamide

The title compound was prepared by substituting EXAMPLE 179A for EXAMPLE 1A in EXAMPLE 1B.



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## Example 179C

Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 179B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (br s, 1H), 8.55 (d, 1H), 8.20 (d, 1H), 8.04 (d, 1H), 7.82-7.76 (m, 2H), 7.53-7.46 (m, 3H), 7.35 (d, 2H), 7.16 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.57 (m, 2H), 3.07 (br s, 4H), 2.75 (br s, 2H), 2.28-2.10 (m, 6H), 2.03-1.94 (m, 4H), 1.83 (d, 2H), 1.80 (s, 3H), 1.55-1.24 (m, 6H), 0.92 (s, 6H).

## Example 180

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoro ethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 180A

(R)-tert-butyl  
1-(2,2-difluoroethyl)pyrrolidin-3-ylcarbamate

To a solution of (R)-tert-butyl pyrrolidin-3-ylcarbamate (500 mg) and 1,1-difluoro-2-iodoethane (618 mg) in N,N-dimethylformamide (6 mL) was added N-ethyl-N-isopropylpropan-2-amine (1.403 mL) and the mixture was stirred at 70° C. for 72 hours. The reaction mixture was concentrated and the crude product was purified on silica gel with methanol/dichloromethane.

## Example 180B

(R)-1-(2,2-difluoroethyl)pyrrolidin-3-amine

To a solution of EXAMPLE 180A (525 mg) in a mixture of dichloromethane (3 mL) and methanol (4.0 mL) was added hydrogen chloride, 4M in dioxane (5.24 mL) and the reaction was stirred for 1.5 hours. The reaction was concentrated and the crude material was taken up in dichloromethane and the solvent evaporated, then taken up in ether and the solvent evaporated, and then dried on high vacuum.

## Example 180C

(R)-4-(1-(2,2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 180B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 180D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoro ethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 180C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (m, 1H), 9.27 (d, 1H), 8.55 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.10 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.04-6.29 (m, 1H), 4.06 (m, 1H), 3.07 (m, 4H), 2.83-2.95 (m, 4H), 2.74-2.82 (m, 3H), 2.47 (m, 1H), 2.09-2.30 (m, 8H), 1.97 (s, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 181

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoro ethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 181A

(S)-tert-butyl  
1-(2-fluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 1-fluoro-2-iodoethane for 1,1-difluoro-2-iodoethane and (S)-tert-butyl pyrrolidin-3-ylcarbamate for (R)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 180A.

## Example 181B

(S)-1-(2-fluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 181A for EXAMPLE 180A in EXAMPLE 180B.

## Example 181C

(S)-4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 181B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 181D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoro ethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 181C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (m, 1H), 9.26 (d, 1H), 8.56 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.63-7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.60 (t, 1H), 4.51 (t, 1H), 4.05 (m, 1H), 3.07 (m, 4H), 2.84 (m, 1H), 2.66-2.79 (m,

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6H), 2.39 (q, 1H), 2.20-2.29 (m, 3H), 2.15 (m, 5H), 1.97 (s, 2H), 1.66 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 182

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 182A

(S)-tert-butyl 1-(2,2-difluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylcarbamate for (R)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 180A.

## Example 182B

(S)-1-(2,2-difluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 182A for EXAMPLE 180A in EXAMPLE 180B.

## Example 182C

(S)-4-(1-(2,2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 182B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 182D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 182C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (m, 1H), 9.27 (d, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.04-6.29 (m, 1H), 4.06 (m, 1H), 3.07 (m, 4H), 2.83-2.95 (m, 4H), 2.74-2.82 (m, 3H), 2.47 (m, 1H), 2.09-2.30 (m, 8H), 1.97 (s, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 183

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 183A

(R)-tert-butyl 1-(2-fluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 1-fluoro-2-iodoethane for 1,1-difluoro-2-iodoethane in EXAMPLE 180A.

## Example 183B

(R)-1-(2-fluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 183A for EXAMPLE 180A in EXAMPLE 180B.

## Example 183C

(R)-4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 183B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 183D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 183C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (m, 1H), 9.26 (d, 1H), 8.56 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.63-7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.60 (t, 1H), 4.50 (t, 1H), 4.04 (m, 1H), 3.07 (m, 4H), 2.84 (m, 1H), 2.66-2.79 (m, 6H), 2.39 (q, 1H), 2.19-2.28 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.66 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 184

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-yl]pyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 184A

(S)-tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate

To a solution of (S)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (0.300 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.238 g). After stirring for 15 minutes,

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4-fluoro-3-nitrobenzenesulfonamide (0.295 g) was added and reaction stirred at room temperature. After 1 hour, the reaction was partitioned between water (25 mL) and dichloromethane (50 mL) and the reaction quenched with 1N aqueous HCl (5.96 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 12 g) eluting with a gradient of 0.2% to 2% methanol/dichloromethane over 30 minutes (flow=36 mL/minute) gave the title compound.

**Example 184B**

(S)-3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methoxy)benzenesulfonamide

To (S)-tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate (0.433 g) was added hydrogen chloride (4.0M in dioxane, 1.0 mL). After stirring for 1 hour, the reaction was concentrated and partitioned between dichloromethane (50 mL) and saturated aqueous NaHCO<sub>3</sub> solution (50 mL). The aqueous layer was separated and concentrated. The residue was triturated with methanol (100 mL), filtered and concentrated and treated with sodium cyanoborohyde (0.068 g) and cyclobutanone (0.078 g) and stirred overnight. The reaction was partitioned between dichloromethane (50 mL) and water (25 mL) and saturated aqueous NaHCO<sub>3</sub> (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

**Example 184C**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-((3S)-1-oxetan-3-ylpyrrolidin-3-yl)methoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 184B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 11.45-11.01 (m, 1H), 8.30 (d, 1H), 7.98 (dd, 2H), 7.60-7.43 (m, 3H), 7.33 (t, 3H), 7.04 (d, 2H), 6.74-6.59 (m, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.49 (td, 2H), 4.33 (s, 1H), 4.13 (dd, 2H), 3.79 (s, 2H), 3.44 (dd, 2H), 3.07 (s, 4H), 2.74 (d, 6H), 2.19 (d, 6H), 1.98 (d, 2H), 1.74-1.52 (m, 1H), 1.39 (t, 2H), 0.92 (s, 6H).

**Example 185**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-[(4-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (4-hydroxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 11.67 (bs, 1H), 9.32 (d, 1H), 9.14 (s, 1H), 8.44 (d, 1H), 8.28 (dd, 1H), 8.09 (d, 1H), 7.65-7.68 (m, 2H), 7.44 (d, 2H), 7.37-7.41 (m, 2H), 7.19 (s, 2H), 7.07 (d, 2H), 6.93 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.54 (d, 2H), 3.02-3.09 (m, 4H), 2.77 (s, 2H), 2.22-2.29 (m, 2H), 2.10-2.17 (m, 4H), 1.97 (d, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

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4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-[(3-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-hydroxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 11.67 (bs, 1H), 9.27-9.32 (m, 2H), 8.43 (d, 1H), 8.20 (dd, 1H), 8.08 (d, 1H), 7.66 (t, 2H), 7.44 (d, 2H), 7.33 (t, 1H), 7.25 (s, 1H), 7.13 (dd, 1H), 7.07 (d, 2H), 6.98 (d, 1H), 6.88 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.64 (d, 2H), 3.02-3.09 (m, 4H), 2.77 (s, 2H), 2.22-2.28 (m, 2H), 2.09-2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 187**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-[(3-difluoromethoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-difluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.34 (t, 1H), 9.30 (d, 1H), 8.42 (d, 1H), 8.26 (dd, 1H), 8.08 (d, 1H), 7.66 (ddd, 2H), 7.40-7.45 (m, 3H), 7.36 (t, 1H), 7.27-7.30 (m, 2H), 7.19 (d, 1H), 7.07 (d, 2H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.69 (d, 2H), 3.02-3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.09-2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 188**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([cis-3-morpholin-4-ylcyclopentyl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 188A**

Cis-methyl 3-morpholinocyclopentanecarboxylate

The title compound was prepared by substituting methyl 3-oxocyclopentanecarboxylate for 4'-chlorobiphenyl-2-carboxaldehyde and morpholine for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

**Example 188B**

Cis-3-morpholinocyclopentyl)methanol

The title compound was prepared by substituting EXAMPLE 188A for EXAMPLE 101C in EXAMPLE 101D.

**Example 188C**

4-((Cis-3-morpholinocyclopentyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 188B for (1,4-dioxan-2-yl)methanol in EXAMPLE 12A.

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## Example 188D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 188C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.57 (s, 1H), 8.17 (m, 1H), 7.94 (m, 1H), 7.82 (m, 1H), 7.56 (d, 1H), 7.44 (t, 1H), 7.34 (m, 3H), 7.16 (m, 1H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.24 (d, 1H), 4.06 (m, 2H), 3.62 (m, 4H), 3.03 (m, 4H), 2.75 (s, 2H), 2.35 (m, 2H), 2.19 (m, 6H), 2.03 (m, 2H), 1.96 (s, 2H), 1.78 (m, 2H), 1.51 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H)

## Example 189

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 189A

Trans-(4-Methanesulfonylamino-cyclohexyl)-carbamic acid tert-butyl ester

The title compound was prepared by substituting methanesulfonyl chloride for acetyl chloride in EXAMPLE 179A.

## Example 189B

Trans-N-(4-Aminocyclohexyl)-methanesulfonamide

The title compound was prepared by substituting EXAMPLE 189A for EXAMPLE 1A in EXAMPLE 1B.

## Example 189C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 189B for 1-acetyl piperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (br s, 1H), 8.55 (d, 1H), 8.18 (d, 1H), 8.04 (d, 1H), 7.84 (d, 1H), 7.79 (dd, 1H), 7.56-7.47 (m, 3H), 7.34 (d, 2H), 7.16 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.56 (m, 1H), 3.17 (m, 1H), 3.07 (br s, 4H), 2.93 (s, 3H), 2.75 (br s, 2H), 2.28-2.10 (m, 6H), 2.05-1.90 (m, 6H), 1.55-1.32 (m, 6H), 0.92 (s, 6H).

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## Example 190

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 190A

4-(1-cyclopropylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 17A by replacing (tetrahydropyran-4-yl)methylamine with 4-amino-1-cyclopropylpiperidine.

## Example 190B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 3J and EXAMPLE 190A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.13 (d, 1H), 8.02 (d, 1H), 7.91 (m, 1H), 7.48 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (m, 2H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.64 (m, 1H), 3.13 (m, 5H), 2.73 (m, 5H), 2.22 (m, 6H), 1.92 (m, 5H), 1.70 (m, 1H), 1.41 (m, 5H), 0.94 (s, 6H), 0.41 (m, 4H).

## Example 191

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 191A

3-nitro-4-(piperidin-4-ylmethoxy)benzenesulfonamide

To a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (0.300 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.223 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.276 g) was added and reaction stirred at room temperature. After 1 hour the reaction was partitioned between water (25 mL) and dichloromethane (50 mL) and the reaction quenched with 1N aqueous HCl (5.57 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Treatment with HCl (4.0M in dioxane, 2 mL) and methanol (2 mL) for 1 hour, followed by concentration, titration with dichloromethane and filtration gave the title compound.

## Example 191B

3-nitro-4-((1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a suspension of 3-nitro-4-(piperidin-4-ylmethoxy)benzenesulfonamide (0.100 g) and cyclobutanone (0.030 g) in



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methanol (1 mL) was added sodium cyanoborohydride (0.027 g). After stirring overnight, the reaction was quenched with saturated NaHCO<sub>3</sub> (5 mL) and extracted into dichloromethane (2×10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

## Example 191C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 191B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 11.46-10.46 (m, 1H), 8.29 (s, 1H), 8.00 (d, 2H), 7.61-7.41 (m, 3H), 7.35 (d, 3H), 7.04 (d, 2H), 6.66 (d, 1H), 6.37 (s, 1H), 6.21 (s, 1H), 4.67-4.40 (m, 4H), 4.08 (d, 2H), 3.06 (s, 4H), 2.78 (s, 4H), 2.19 (m, 6H), 1.96 (s, 4H), 1.79 (m, 4H), 1.39 (s, 4H), 0.93 (s, 6H).

## Example 192

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 192A

4-((4-fluoro-1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

A mixture of EXAMPLE 173A (0.4 g), dihydro-2H-pyran-4(3H)-one (0.179 g), sodium cyanoborohydride (0.112 g), and acetic acid (0.5 mL) in tetrahydrofuran (3 mL) was stirred overnight. The solvents were removed under reduced pressure. The residue was purified with flash column chromatography on silica gel eluting with 100:5:0.5 ethyl acetate/methanol/NH<sub>4</sub>OH to give the desired product.

## Example 192B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 192A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.25 (s, 1H), 7.96 (d, 1H), 7.93 (d, 1H), 7.57 (d, 1H), 7.45 (t, 1H), 7.34-7.37 (m, 3H), 7.26 (d, 1H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.34 (dd, 1H), 6.23 (d, 1H), 4.34 (d, 2H), 3.93 (dd, 2H),

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3.03 (s, 6H), 2.76 (s, 4H), 2.09-2.22 (m, 6H), 1.96 (s, 2H), 1.52-1.27 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 193

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 193A

4-((4-fluoro-1-(tetrahydrofuran-3-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting dihydrofuran-3(2H)-one for dihydro-2H-pyran-4(3H)-one in EXAMPLE 192A.

## Example 193B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 193A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.31 (s, 1H), 7.99-8.00 (m, 2H), 7.54 (d, 1H), 7.46-7.48 (m, 2H), 7.34-7.35 (m, 3H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.34 (d, 2H), 3.76-3.83 (m, 3H), 3.62-3.65 (m, 2H), 3.03 (s, 4H), 2.79 (s, 4H), 2.24 (s, 2H), 2.15 (s, 2H), 1.84-1.99 (m, 8H), 1.52-1.27 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 194

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 194A

4-((4-fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

A mixture of EXAMPLE 173A (0.4 g), methanesulfonyl chloride (0.113 g), and triethylamine (0.64 mL) in dichloromethane (5 mL) was stirred overnight. The reaction mixture was loaded onto a silica gel column and eluted with 100:1 ethyl acetate:methanol to give the clean product.

## Example 194B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 194A for EXAMPLE 11B in EXAMPLE 11D.

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<sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.37 (s, 1H), 8.06 (d, 1H), 8.02 (d, 1H), 7.49-7.53 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38-6.39 (m, 1H), 6.21 (d, 1H), 4.40 (d, 2H), 3.51-3.54 (m, 2H), 3.09 (s, 4H), 2.96-3.01 (m, 4H), 2.92 (s, 3H), 2.82 (s, 2H), 2.25-2.34 (m, 4H), 2.13-2.16 (m, 6H), 2.01-2.07 (m, 2H), 1.99 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 195**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[3-nitro-4-((3R)-1-oxetan-3-ylpyrrolidin-3-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 195A**

(R)-tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate for 1-acetylpiperidin-4-amine in EXAMPLE 53B.

**Example 195B**

(S)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(pyrrolidin-3-ylmethylamino)phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 195A for EXAMPLE 1A in EXAMPLE 1B.

**Example 195C**

(R)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-((1-oxetan-3-yl)pyrrolidin-3-yl)methylamino)phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 195B for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.81 (t, 1H), 8.55 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.35 (m, 2H), 7.04 (m, 3H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.57 (m, 2H), 4.48 (m, 2H), 3.68 (m, 2H), 3.30 (m, 2H), 3.06 (m, 4H), 2.74 (m, 3H), 2.56 (m, 3H), 2.44 (m, 1H), 2.18 (m, 5H), 1.95 (m, 3H), 1.58 (m, 1H), 1.36 (m, 2H), 0.94 (s, 6H).

**Example 196**

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-(4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 196A**

Trans-4-(4-(tert-butyl(dimethylsilyloxy)cyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol

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with trans-(4-(tert-butyl(dimethylsilyloxy)cyclohexyl)methanol (made according to the procedures in WO 2008/124878).

**Example 196B**

Trans-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(((1r,4r)-4-(tert-butyl(dimethylsilyloxy)cyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

The title compound was prepared as described in EXAMPLE 1G using EXAMPLE 196A in place of EXAMPLE 1F and EXAMPLE 3J in place of EXAMPLE 1E.

**Example 196C**

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-(4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 196B (150 mg) in dichloromethane (5 mL) and methanol (2 mL) was treated with 10% aqueous HCl (3 mL) for 1 hour and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (30 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.27 (s, 1H), 8.34 (d, 1H), 7.95-8.08 (m, 2H), 7.47-7.55 (m, 3H), 7.32-7.40 (m, 3H), 7.01-7.07 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.54 (d, 1H), 3.96-4.06 (m, 2H), 3.10 (s, 4H), 2.84 (s, 2H), 2.05-2.39 (m, 6H), 1.96 (s, 2H), 1.46-1.93 (m, 5H), 1.39 (t, 2H), 0.98-1.29 (m, 4H), 0.92 (s, 6H).

**Example 197**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 197A**

3-(4-(aminomethyl)phenoxy)-N,N-dimethylpropan-1-amine

4-(3-(Dimethylamino)propoxy)benzonitrile (300 mg) in methanol (20 mL) was treated with Raney nickel (wet, 1.5 g) under H<sub>2</sub> (30 psi) for 4 hour. The insoluble material was filtered off and the filtrate was concentrated to provide the title compound.

**Example 197B**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using EXAMPLE 197A in place of

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EXAMPLE 120A. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.80 (t, 1H), 8.42 (d, 1H), 7.93 (d, 1H), 7.52-7.61 (m, 2H), 7.41-7.47 (m, 1H), 7.26-7.36 (m, 5H), 7.03-7.08 (m, 2H), 6.89 (d, 2H), 6.73 (d, 1H), 6.61 (dd, 1H), 6.31 (dd, 1H), 6.22 (d, 1H), 4.52 (d, 2H), 3.99 (t, 2H), 2.90-3.05 (m, 7H), 2.72 (s, 2H), 2.61 (s, 6H), 2.09-2.24 (m, 6H), 1.89-2.04 (m, 5H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 198

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 198A

(4-(2-morpholinoethoxy)phenyl)methanamine

The title compound was prepared as described in EXAMPLE 197A using 4-(2-morpholinoethoxy)benzonitrile in place of 4-(3-(dimethylamino)propoxy)benzonitrile.

## Example 198B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-morpholin-4-ylethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using EXAMPLE 198A in place of EXAMPLE 120A. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 9.00 (t, 1H), 8.56 (d, 1H), 8.02 (d, 1H), 7.72 (dd, 1H), 7.46-7.54 (m, 3H), 7.27-7.36 (m, 4H), 7.01-7.07 (m, 2H), 6.89-6.95 (m, 3H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.18 (d, 1H), 4.56 (d, 2H), 4.07 (t, 2H), 3.54-3.61 (m, 4H), 3.06 (s, 4H), 2.71-2.78 (m, 4H), 2.07-2.24 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 199

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 199A

4-[(E)-4-Hydroxy-adamantan-1-ylmethyl]-amino]-3-nitro-benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (0.5 g) and 5-(aminomethyl)adamantan-2-ol (0.6 g) in tetrahydrofuran (10 mL) were treated with triethylamine (1 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC, eluting 40-60% acetonitrile in 0.1 trifluoroacetic acid water to give two isomers, which were temporarily assigned as EXAMPLE 199A and EXAMPLE 199B, respectively.

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## Example 199B

4-[(Z)-4-Hydroxy-adamantan-1-ylmethyl]-amino]-3-nitro-benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (0.5 g) and 5-(aminomethyl)adamantan-2-ol (0.6 g) in tetrahydrofuran (10 mL) were treated with triethylamine (1 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC, eluting 40-60% acetonitrile in 0.1 trifluoroacetic acid water to give two isomers, which were temporarily assigned as EXAMPLE 199A and EXAMPLE 199B, respectively.

## Example 199C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 199A in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.40 (s, 1H), 8.55 (d, 1H), 8.50 (t, 1H), 8.03 (d, 1H), 7.77 (dd, 1H), 7.46-7.54 (m, 3H), 7.31-7.38 (m, 2H), 7.14 (d, 1H), 7.01-7.06 (m, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 4.61 (d, 1H), 3.63 (d, 1H), 3.02-3.16 (m, 6H), 2.75 (s, 2H), 2.17 (d, 6H), 2.04 (d, 2H), 1.95 (s, 2H), 1.76-1.88 (m, 3H), 1.49-1.61 (m, 6H), 1.38 (t, 2H), 1.29 (d, 2H), 0.92 (s, 6H).

## Example 200

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 199B in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.39 (s, 1H), 8.55 (d, 1H), 8.51 (t, 1H), 8.04 (d, 1H), 7.77 (dd, 1H), 7.46-7.55 (m, 3H), 7.31-7.37 (m, 2H), 7.14 (d, 1H), 7.01-7.06 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.61 (d, 1H), 3.61 (d, 1H), 3.08 (d, 6H), 2.75 (s, 2H), 2.17 (d, 6H), 1.79-1.99 (m, 7H), 1.55-1.69 (m, 4H), 1.49 (s, 2H), 1.38 (t, 2H), 1.22 (d, 2H), 0.92 (s, 6H).

## Example 201

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 201A

4-((1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with (1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethanol.

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## Example 201B

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-yl-methoxy]-3-nitrophenyl}sulfonyl)-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 201A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.35 (d, 1H), 7.95-8.10 (m, 2H), 7.47-7.58 (m, 3H), 7.30-7.45 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (d, 1H), 5.92-6.23 (m, 3H), 3.65-4.39 (m, 3H), 3.00-3.22 (m, 4H), 2.76-2.98 (m, 4H), 2.28 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.71-1.91 (m, 1H), 1.33-1.47 (m, 3H), 1.20-1.32 (m, 2H), 0.92 (s, 6H), 0.50-0.66 (m, 1H).

## Example 202

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 82 (140 mg) was dissolved in dioxane (3.0 mL), and 4-amino-1-methylpyrrolidin-2-one hydrochloride (30 mg) and triethylamine (0.100 mL) were added. The reaction mixture was heated at 110° C. for 40 hours. The reaction was concentrated and the crude material was purified by preparative HPLC using a C18 column, 250x50 mm, 10μ, and eluting with a gradient of 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.74 (d, 1H), 8.37 (br d, 1H), 8.02 (d, 1H), 7.83 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.21 (d, 1H), 4.46 (m, 1H), 3.81 (dd, 1H), 3.38 (dd, 1H), 3.08 (br m, 4H), 2.82 (dd, 1H), 2.75 (s, 5H), 2.43 (dd, 1H), 2.21 (br m, 4H), 2.16 (br t, 2H), 1.95 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 203

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 203A

4-(((1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 201A (340 mg) in tetrahydrofuran (10 mL) and water (1 mL) was added N-methylmorpholine N-oxide (184 mg) and OsO<sub>4</sub> (2.5% in 2-methyl-2-propanol) (1.05 mL). The reaction mixture was stirred overnight and purified by reverse phase HPLC to provide two isomers, which were temporarily assigned as EXAMPLE 203A and EXAMPLE 203B, respectively.

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## Example 203B

4-(((1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 201A (340 mg) in tetrahydrofuran (10 mL) and water (1 mL) was added N-methylmorpholine N-oxide (184 mg) and OsO<sub>4</sub> (2.5% in 2-methyl-2-propanol) (1.05 mL). The reaction mixture was stirred overnight and purified by reverse phase HPLC to provide two isomers, which were temporarily assigned as EXAMPLE 203A and EXAMPLE 203B, respectively.

## Example 203C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 203A in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.33 (s, 1H), 7.97-8.07 (m, 2H), 7.48-7.55 (m, 3H), 7.41 (d, 1H), 7.32-7.37 (m, 2H), 7.02-7.07 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.58 (dd, 2H), 4.07-4.19 (m, 2H), 3.82 (t, 1H), 3.51 (t, 1H), 3.09 (s, 4H), 2.81 (s, 2H), 2.09-2.34 (m, 8H), 2.04-2.09 (m, 2H), 1.93-2.01 (m, 3H), 1.62-1.77 (m, 2H), 1.39 (t, 2H), 1.11 (d, 1H), 0.92 (s, 6H), 0.67-0.76 (m, 1H).

## Example 204

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 203B in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.33 (s, 1H), 7.98-8.07 (m, 2H), 7.49-7.54 (m, 3H), 7.41 (d, 1H), 7.32-7.36 (m, 2H), 7.02-7.07 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.58 (dd, 2H), 4.13 (dd, 2H), 3.82 (t, 1H), 3.51 (t, 1H), 3.09 (s, 4H), 2.81 (s, 2H), 2.09-2.35 (m, 8H), 2.07 (s, 2H), 1.93-2.02 (m, 3H), 1.61-1.80 (m, 2H), 1.39 (t, 2H), 1.11 (d, 1H), 0.92 (s, 6H), 0.66-0.78 (m, 1H).

## Example 205

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 205A

Methyl 1,4-dioxaspiro[4.5]decane-7-carboxylate

To a solution of trimethylsilyltrifluoromethanesulfonate (0.034 mL) in dry dichloromethane (5 mL) was added 1,2-bis(trimethylsiloxy)ethane (4.55 mL) followed by methyl 3-oxocyclohexanecarboxylate (2.9 g). The reaction mixture was stirred for 3 hours at -78° C. The reaction mixture was



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quenched with dry pyridine (0.5 mL), poured into saturated aqueous NaHCO<sub>3</sub>, and extracted with ether. The ether layer was dried over Na<sub>2</sub>CO<sub>3</sub>/Na<sub>2</sub>SO<sub>4</sub>. The reaction mixture was concentrated and purified by flash chromatography on silica with 5 to 30% ethyl acetate in hexanes to provide the title compound.

## Example 205B

## 1,4-dioxaspiro[4.5]decan-7-ylmethanol

The title compound was prepared by substituting EXAMPLE 205A for EXAMPLE 101C in EXAMPLE 101D.

## Example 205C

## 3-nitro-4-((3-oxocyclohexyl)methoxy)benzene-sulfonamide

Into a 250 mL round-bottomed flask was added sodium hydride (0.5 g) in tetrahydrofuran (10 mL) and then 1,4-dioxaspiro[4.5]decan-7-ylmethanol (0.5 g) was added. After the mixture stirred at room temperature for 20 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.65 g) was added. The mixture was stirred at room temperature for overnight. Water (20 mL) was added slowly. The aqueous layer was extracted by dichloromethane (3×20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, and concentration of the filtrate, the residue was purified by reverse phase chromatography, eluting with 30-60% acetonitrile in water with 0.1% trifluoroacetic acid.

## Example 205D

## 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((3-oxocyclohexyl)methoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 205C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.22 (s, 1H), 7.96 (d, 1H), 7.87 (m, 1H), 7.55 (d, 1H), 7.45 (t, 1H), 7.35 (m, 3H), 7.20 (m, 1H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.23 (d, 1H), 4.07 (d, 2H), 3.04 (m, 4H), 2.76 (s, 2H), 2.35 (m, 2H), 2.20 (m, 8H), 1.96 (m, 4H), 1.58 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 206

## 4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 206A

## 2-chloro-5,5-dimethylcyclohexa-1,3-dienecarbaldehyde

In a 250 mL round-bottomed flask was added N,N-dimethylformamide (3.5 mL) in dichloromethane (30 mL), and the mixture was cooled to -10° C. Phosphoryl trichloride (4 mL) was added dropwise, and the solution was warmed up to room temperature. 4,4-Dimethylcyclohex-2-enone (5.5 mL) was

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then added slowly, and the mixture was heated to reflux overnight. The reaction mixture was cooled and quenched with a 0° C. solution of sodium acetate (25 g in 50 mL water). The aqueous layer was extracted with diethyl ether (200 mL×3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 206B

## 2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienecarbaldehyde

Into a 1 L round-bottomed flask was added EXAMPLE 206A (6.8 g), 4-chlorophenylboronic acid (6.5 g), and palladium (II) acetate (0.2 g) in water (100 mL) to give a suspension. Potassium carbonate (15 g) and tetrabutylammonium bromide (10 g) were added. After degassing, the mixture was stirred at 45° C. for 4 hours. After cooling and filtering through silica gel in a funnel, diethyl ether (4×200 mL) was used to extract the product. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was concentrated and purified by flash chromatography on silica with 0-10% ethyl acetate in hexanes to provide the title compound.

## Example 206C

## Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 206B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 206D

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 206C for EXAMPLE 101E in EXAMPLE 101F.

## Example 206E

## 4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 206D for EXAMPLE 3J and EXAMPLE 1F for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (s, 1H), 8.49 (m, 2H), 7.99 (m, 1H), 7.72 (m, 1H), 7.53 (d, 1H), 7.41 (m, 4H), 7.12 (d, 2H), 6.99 (m, 1H), 6.66 (dd, 1H), 6.35 (m, 1H), 6.23 (d, 1H), 5.74 (d, 1H), 5.58 (d, 1H), 3.84 (m, 2H), 3.26 (m, 4H), 3.06 (m, 4H), 2.88 (s, 2H), 2.24 (m, 6H), 1.61 (m, 2H), 1.26 (m, 3H), 1.00 (s, 6H).

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## Example 207

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 207A

(R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-amine

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl azetidin-3-ylcarbamate in EXAMPLE 151A.

## Example 207B

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 207A for EXAMPLE 151A in EXAMPLE 151B.

## Example 207C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 207B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.52-11.24 (m, 1H), 8.55 (d, 1H), 8.37 (d, 1H), 8.03 (d, 1H), 7.83 (dd, 1H), 7.57-7.45 (m, 3H), 7.34 (d, 2H), 7.06 (t, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.70 (d, 2H), 4.54 (d, 2H), 4.23 (s, 1H), 3.11-2.87 (m, 7H), 2.74 (dd, 4H), 2.35-2.13 (m, 7H), 1.95 (s, 2H), 1.70 (s, 1H), 1.39 (d, 2H), 0.92 (s, 6H).

## Example 208

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 208A

2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-iodo-3-(trifluoromethyl)pyridine

A mixture of EXAMPLE 37C (0.537 g), 5-iodo-3-(trifluoromethyl)pyridin-2-ol (1.156 g), and triphenylphosphine (1.574 g) in tetrahydrofuran (20 mL) was cooled to 0° C. To this solution was added (E)-di-tert-butyl diazene-1,2-dicarboxylate (0.921 g). The reaction mixture was stirred overnight. The solvent was removed, and the residue was purified

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with column flash chromatography on silica gel eluting with 4:1 hexanes/ethyl acetate to give the desired product.

## Example 208B

6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

EXAMPLE 207A (1.3 g) in tetrahydrofuran (10 mL) was cooled to -42° C. with a cold bath of CH<sub>3</sub>CN/dry ice. To this solution was added 2.0 M isopropylmagnesium chloride (1.6 mL) dropwise over 5 minutes. The reaction mixture was stirred for 30 minutes at -42° C., then allowed to warm to 0° C. over 10 minutes. The reaction mixture was cooled again to -42° C., and SO<sub>2</sub> was bubbled through it for 10 minutes. The reaction mixture was stirred for another 30 minutes. To this solution was sulfuric dichloride (0.433 g). On warming to room temperature, concentrated NH<sub>4</sub>OH (10 mL) was added and the reaction mixture was stirred for another 2 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 3:1 hexanes/ethyl acetate to give the title compound.

## Example 208C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 208B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (s, 1H), 8.72 (s, 1H), 8.36 (s, 1H), 7.98 (d, 1H), 7.55 (d, 1H), 7.42-7.47 (m, 2H), 7.36 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.35 (s, 1H), 6.23 (s, 1H), 4.56 (d, 2H), 3.75-3.79 (m, 2H), 3.56-3.61 (m, 2H), 3.09 (s, 4H), 2.32-2.37 (m, 2H), 2.16 (s, 2H), 1.97-1.99 (m, 2H), 1.79-1.86 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

## Example 209

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 209A

(S)-tert-butyl (1-(oxetan-3-yl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 209B

(S)-1-(oxetan-3-yl)pyrrolidin-3-ylmethanamine

The title compound was prepared by substituting EXAMPLE 209A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

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## Example 209C

(S)-3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and EXAMPLE 209B for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 209D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((3S)-1-oxetan-3-ylpyrrolidin-3-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 209C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.30 (d, 1H), 9.02 (t, 1H), 8.42 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.67 (dd, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (m, 1H), 6.52 (m, 2H), 4.82 (t, 1H), 4.75 (t, 1H), 4.67 (t, 2H), 3.57 (m, 1H), 3.24 (t, 2H), 3.07 (m, 4H), 2.75 (m, 3H), 2.57 (dd, 1H), 2.45 (s, 1H), 2.36 (t, 1H), 2.26 (s, 2H), 2.18 (m, 5H), 1.93 (m, 3H), 1.56 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 210

Trans-N-([5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 210A

(4-methoxycyclohexyl)methanol

The title compound was prepared by substituting 4-methoxycyclohexanecarboxylic acid for 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate in EXAMPLE 126A.

## Example 210B

Trans-5-chloro-6-((4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 210A for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 210C

Trans-N-([5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 210C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H), 7.49-7.54 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.39 (s, 1H), 6.21

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(s, 1H), 4.20 (d, 2H), 3.23 (s, 3H), 3.06-3.09 (m, 4H), 2.15-2.37 (m, 4H), 1.96-2.03 (m, 4H), 1.74-1.84 (m, 2H), 1.40 (t, 2H), 1.04-1.13 (m, 4H), 0.93 (s, 6H).

## Example 211

Cis-N-([5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 211A

Cis-5-chloro-6-((4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was isolated as a by-product in the synthesis of EXAMPLE 210B.

## Example 211B

Cis-N-([5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 211A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.03 (d, 1H), 7.49-7.54 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (s, 1H), 6.21 (s, 1H), 4.21 (d, 2H), 3.20 (s, 3H), 3.06 (s, 4H), 2.15-2.37 (m, 4H), 1.96 (s, 2H), 1.80-1.84 (m, 2H), 1.50-1.54 (m, 2H), 1.34-1.44 (m, 6H), 0.93 (s, 6H).

## Example 212

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((3S)-1-oxetan-3-ylpyrrolidin-3-yl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 212A

(S)-tert-butyl 1-(oxetan-3-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 212B

(S)-1-(oxetan-3-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 212A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

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## Example 212C

(S)-3-nitro-4-(1-(oxetan-3-yl)pyrrolidin-3-ylamino) benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and EXAMPLE 212B for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 212D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 212C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.58 (d, 1H), 8.42 (d, 1H), 8.37 (dd, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.67 (m, 4H), 4.09 (m, 1H), 3.59 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.69 (m, 2H), 2.62 (dd, 1H), 2.28 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.68 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 213

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 213A

4-((4-(2-(2-methoxyethoxy)ethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(2'-methoxyethoxy)ethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 213B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 213A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.98 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.96-3.86 (m, 2H), 3.72 (dd, 1H), 3.67-3.61 (m, 4H), 3.51 (t, 2H), 3.48-3.38 (m, 2H), 3.28 (s, 3H), 3.07 (m, 4H), 2.95 (d, 1H), 2.77 (s, 2H), 2.70 (m, 1H), 2.60 (t, 2H), 2.30-2.05 (m, 8H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

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## Example 214

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-(cyanomethyl)morpholin-2-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 214A

4-((4-(cyanomethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

## Example 214B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-(cyanomethyl)morpholin-2-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 214A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.93 (m, 1H), 3.87 (d, 1H), 3.77 (s, 2H), 3.65 (dt, 1H), 3.51-3.40 (m, 2H), 3.07 (m, 4H), 2.87 (d, 1H), 2.77 (s, 2H), 2.60 (d, 1H), 2.50 (m, 1H), 2.38 (t, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 215

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-(N,N-dimethylglycyl)morpholin-2-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 215A

4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-dimethylaminoacetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

## Example 215B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-(N,N-dimethylglycyl)morpholin-2-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 215A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd,



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1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 216**

(2-({(4-({(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl}-2-nitrophenyl)amino)methyl}morpholin-4-yl)acetic acid

**Example 216A**

tert-butyl 2-(2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholino)acetate

The title compound was prepared by substituting tert-butyl 2-bromoacetate for methyl iodide in EXAMPLE 134B.

**Example 216B**

tert-butyl 2-(2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholino)acetate

The title compound was prepared by substituting EXAMPLE 216A for EXAMPLE 130C in EXAMPLE 130D.

**Example 216C**

(2-({(4-({(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl}-2-nitrophenyl)amino)methyl}morpholin-4-yl)acetic acid

The title compound was prepared by treating EXAMPLE 216B with 50% trifluoroacetic acid in dichloromethane. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.97 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.30 (dd, 1H), 8.12 (d, 1H), 7.69 (t, 1H), 7.64 (d, 1H), 7.43 (d, 2H), 7.08 (d, 2H), 6.88 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 6.47 (m, 1H), 4.05-4.00 (m, 1H), 3.91 (d, 1H), 3.79 (dt, 1H), 3.50 (s, 2H), 3.45 (m, 2H), 3.13 (d, 1H), 3.07 (m, 4H), 2.88 (d, 1H), 2.78 (s, 2H), 2.57 (dt, 1H), 2.43 (t, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 217**

4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl)methyl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 217A**

The title compound was prepared by substituting EXAMPLE 134A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

**356****Example 217B**

4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl)methyl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 217A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.64 (m, 4H), 3.93 (m, 1H), 3.89 (d, 1H), 3.68 (dt, 1H), 3.53-3.35 (m, 3H), 3.07 (m, 4H), 2.77 (s, 2H), 2.72 (d, 1H), 2.44 (d, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.85 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 218**

4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({(4-({(4-cyclopropylmorpholin-2-yl)methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 218A**

4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 134A for EXAMPLE 173A in EXAMPLE 173B.

**Example 218B**

4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({(4-({(4-cyclopropylmorpholin-2-yl)methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 218A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

**Example 219**

4-(4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-yl)-N-({5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 219A**

5-(methylthio)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 36B (0.1 g) and sodium methanethiolate (0.04 g) in N,N-dimethylformamide (2 mL) was

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heated at 80° C. overnight. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

**Example 219B**

5-(methylsulfonyl)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 219A (0.15 g) and 75% methanol/peroxybenzoic acid (0.217 g) in chloroform (4 mL) was stirred at room temperature. The reaction mixture was stirred overnight. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

**Example 219C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-(methylsulfonyl)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 219B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.81 (s, 1H), 8.55 (d, 1H), 8.01 (d, 1H), 7.55 (d, 1H), 7.49-7.50 (m, 2H), 7.37 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 3.88 (dd, 2H), 3.13 (s, 4H), 2.95 (s, 2H), 2.36-2.38 (m, 2H), 2.03-2.16 (m, 4H), 1.97 (s, 3H), 1.66-1.69 (m, 2H), 1.38-1.402 (m, 4H), 0.93 (s, 6H).

**Example 220**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-((trifluoromethyl)sulfonyl)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 220A**

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethylsulfonyl)benzenesulfonamide

To a solution of EXAMPLE 37C (0.500 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.596 g). Additional tetrahydrofuran (25 mL) was added and the mixture stirred for 30 minutes, then 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (1.145 g) was added as a solution in tetrahydrofuran (5 mL). After stirring for 2 hours, the reaction mixture was partitioned between 1N aqueous HCl (50 mL) and dichloromethane (200 mL). The organic layer was dried over

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magnesium sulfate, filtered, and concentrated. The resulting solid was chromatographed over silica gel (Reveleris 80 g) eluting with a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes (flow=40 mL/min) to provide the title compound.

**Example 220B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-((trifluoromethyl)sulfonyl)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 220A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.42 (s, 1H), 8.35-8.22 (m, 1H), 8.01 (s, 1H), 7.49 (d, 4H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (s, 1H), 6.38 (s, 1H), 6.21 (s, 1H), 4.42 (d, 2H), 3.76 (s, 2H), 3.59 (s, 2H), 3.10 (s, 6H), 2.15 (s, 6H), 2.02-1.74 (m, 6H), 1.40 (s, 2H), 0.93 (s, 6H).

**Example 221**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-((4-methyltetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 221A**

4-((4-methyltetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (4-methyltetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

**Example 221B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-((4-methyltetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 221A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.36 (s, 1H), 8.04-8.06 (m, 2H), 7.50-7.53 (m, 3H), 7.41 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.00 (s, 2H), 3.63-3.67 (m, 2H), 3.53-3.58 (m, 2H), 3.09 (s, 4H), 2.82 (s, 2H), 2.27 (s, 2H), 2.15 (s, 2H), 1.58-1.63 (m, 2H), 1.39 (t, 2H), 1.30-1.34 (m, 2H), 1.09 (s, 3H), 0.92 (s, 6H).

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## Example 222

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethyl-  
cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-  
pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-  
2-nitrophenyl)piperazine-1-carboxylate

## Example 222A

ethyl 4-(2-nitro-4-sulfamoylphenyl)piperazine-1-  
carboxylate

The title compound was prepared by substituting ethyl  
piperazine-1-carboxylate for 1-(tetrahydropyran-4-yl)meth-  
ylamine in EXAMPLE 1F.

## Example 222B

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethyl-  
cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-  
pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-  
2-nitrophenyl)piperazine-1-carboxylate

The title compound was prepared by substituting  
EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 222A for  
EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, dim-  
ethylsulfoxide-d<sub>6</sub>) δ 11.52 (br. s, 1H), 8.08 (d, 1H), 7.89 (d, 1H),  
7.59 (m, 2H), 7.43 (t, 1H), 7.35 (d, 2H), 7.23 (d, 1H),  
7.05 (d, 2H), 6.94 (d, 1H), 6.63 (dd, 1H), 6.29 (m, 2H), 4.07  
(q, 2H), 3.47 (m, 4H), 3.17 (d, 2H), 3.00 (m, 8H), 2.73 (s, 2H),  
2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 1.20 (t, 3H), 0.93 (s, 6H).

## Example 223

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-(morpho-  
lin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-  
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 223A

The title compound was prepared by substituting 4-(pip-  
eridin-4-yl)morpholine for 1-(tetrahydropyran-4-yl)meth-  
ylamine in EXAMPLE 1F.

## Example 223B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-({4-[4-(morpho-  
lin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-  
(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 223A for  
EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, dim-  
ethylsulfoxide-d<sub>6</sub>) δ 11.53 (br. s, 1H), 8.05 (d, 1H), 7.91 (d, 1H),  
7.58 (m, 2H), 7.43 (t, 1H), 7.35 (d, 2H), 7.26 (d, 1H),  
7.05 (d, 2H), 6.91 (d, 1H), 6.62 (dd, 1H), 6.29 (m, 2H), 5.76  
(s, 1H), 3.57 (m, 4H), 3.20 (m, 2H), 3.01 (m, 4H), 2.80 (t, 2H),  
2.73 (s, 2H), 2.47 (m, 4H), 2.32 (m, 1H), 2.18 (m, 6H), 1.96  
(m, 3H), 1.82 (m, 2H), 1.44 (m, 4H), 0.93 (s, 6H).

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## Example 224

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-  
{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]  
amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyri-  
din-5-yloxy)benzamide

## Example 224A

(R)-tert-butyl 1-(oxetan-3-yl)pyrrolidin-3-ylcarbam-  
ate

The title compound was prepared by substituting (R)-tert-  
butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-  
carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-car-  
boxaldehyde in EXAMPLE 1A.

## Example 224B

(R)-1-(oxetan-3-yl)pyrrolidin-3-amine

The title compound was prepared by substituting  
EXAMPLE 224A for (S)-1-tert-butyl 2-methyl 4,4-difluoro-  
pyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

## Example 224C

(R)-3-nitro-4-(1-(oxetan-3-yl)pyrrolidin-3-ylamino)  
benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-  
3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzene-  
sulfonamide and EXAMPLE 224B for 4-methylpiperazin-1-  
amine dihydrochloride in EXAMPLE 6A.

## Example 224D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-  
{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]  
amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyri-  
din-5-yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 224C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.26 (d, 1H),  
8.57 (d, 1H), 8.42 (d, 1H), 8.36 (dd, 1H), 8.09 (d, 1H),  
7.66 (m, 1H), 7.64 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.86  
(d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.67 (m, 4H),  
3.58 (m, 1H), 3.07 (m, 4H), 2.77 (m, 2H), 2.68 (m, 2H),  
2.61 (m, 1H), 2.28 (m, 4H), 2.14 (m, 4H), 1.97 (m, 2H), 1.67  
(m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 225

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-  
difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-{(trif-  
luoromethyl)sulfonyl}phenyl)sulfonyl]-2-(1H-  
pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 225A

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-  
ylamino)-3-(trifluoromethylsulfonyl)benzene-  
sulfonamide

To EXAMPLE 207A (0.217 g) and 4-fluoro-3-(trifluorom-  
ethylsulfonyl)benzenesulfonamide (0.281 g) in tetrahydrofu-

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ran (5 mL) was added diisopropylethylamine (0.559 mL) and the reaction was allowed to stir at room temperature for 1 hour and was then heated to 50° C. for 1 hour. The reaction was concentrated, the residue was loaded onto silica gel (Reveleris 40 g) and eluted with a gradient of 0.75% methanol/dichloromethane to 7.5% methanol/dichloromethane to provide the title compound.

**Example 225B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-{(trifluoromethyl)sulfonyl}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 225A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.52-11.23 (m, 1H), 8.17 (d, 1H), 8.04 (d, 1H), 7.95 (d, 1H), 7.54 (d, 1H), 7.53-7.50 (m, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.10-6.97 (m, 4H), 6.67 (d, 1H), 6.40 (dd, 1H), 6.18 (d, 1H), 4.60 (dd, 4H), 4.20 (s, 1H), 3.11-2.63 (m, 12H), 2.19 (d, 6H), 1.95 (s, 2H), 1.58 (s, 1H), 1.40 (d, 2H), 0.92 (s, 6H).

**Example 226**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 226A**

tert-butyl 4-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)piperidine-1-carboxylate

To a solution of EXAMPLE 82 (800 mg) and tert-butyl 4-aminopiperidine-1-carboxylate (203 mg) in dioxane (10 mL) was added Hunig's Base (1 mL). The mixture was stirred at 120° C. overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of solvent, the residue was loaded on a silica gel cartridge and eluted with 3% methanol in dichloromethane to give the title compound.

**Example 226B**

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylamino)phenylsulfonyl)benzamide

To a solution of EXAMPLE 226A (902 mg) in dichloromethane (10 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at room temperature for 3 hours. The mixture was concentrated under vacuum and co-concentrated with dichloromethane twice to afford the crude product which was used in the next step without further purification.

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 226B (79 mg) in tetrahydrofuran (3 mL) and acetic acid (1 mL) was added acetone (54 mg) and MP-cyanoborohydride (150 mg, 2.25 mmol/g). The mixture was stirred overnight. The mixture was filtered. The filtrate was concentrated and the residue was loaded on a silica gel cartridge and eluted with 5 to 10% 7N NH<sub>3</sub> in methanol in dichloromethane to provide the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 12.09 (s, 1H), 8.34 (m, 1H), 7.93 (m, 2H), 7.66 (m, 4H), 7.35 (d, 2H), 7.06 (d, 2H), 6.89 (m, 1H), 6.74 (dd, 1H), 6.59 (dd, 1H), 6.50 (d, 1H), 3.11 (m, 6H), 2.73 (m, 4H), 2.26 (m, 9H), 1.97 (s, 3H), 1.40 (t, 2H), 1.23 (s, 8H), 0.94 (s, 6H).

**Example 227**

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 227A****1-tert-butylpiperidin-4-amine**

To a solution of 1-tert-butylpiperidin-4-one (5.0 g) in methanol (100 mL) and water (10 mL) was added ammonium formate (20.3 g) and 0.5 g of Pd/C (10%). The mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated under vacuum and the residue was diluted with ethyl acetate (500 mL) and washed with water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub> and filtration, the solvent was evaporated under vacuum to provide the title compound.

**Example 227B**

4-(1-tert-butylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

To a mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.2 g) and EXAMPLE 227A (1.56 g) in tetrahydrofuran (20 mL) was added Hunig's Base (6 mL). The mixture was stirred for 3 days. The mixture was diluted with ethyl acetate (300 mL) and water (100 mL) and stirred until the solid disappeared into the solution. The layers were separated and the organic phase was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The combined aqueous layers were extracted again with ethyl acetate and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was evaporated to provide the title compound.

**Example 227C**

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 227B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dim-



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ethylsulfoxide- $d_6$ )  $\delta$  11.51 (s, 1H), 8.43 (d, 1H), 8.04 (m, 1H), 7.93 (d, 1H), 7.72 (m, 1H), 7.56 (dd, 1H), 7.42 (m, 1H), 7.34 (m, 3H), 7.05 (d, 2H), 6.93 (dd, 1H), 6.62 (dd, 1H), 6.28 (m, 1H), 3.04 (m, 6H), 2.73 (s, 3H), 2.25 (m, 9H), 1.95 (s, 2H), 1.68 (m, 2H), 1.32 (m, 9H), 0.93 (s, 6H).

## Example 228

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[1-(2-methoxyethyl)piperidin-3-yl]methyl}amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

## Example 228A

tert-butyl 3-((2-nitro-4-sulfamoylphenylamino)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)piperidine-1-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 228B

3-nitro-4-(piperidin-3-ylmethylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 228A for EXAMPLE 113A in EXAMPLE 134A.

## Example 228C

4-((1-(2-methoxyethyl)piperidin-3-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 228B for EXAMPLE 134A and 2-methoxyethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 228D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[1-(2-methoxyethyl)piperidin-3-yl]methyl}amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared by substituting EXAMPLE 228C for EXAMPLE 130C in EXAMPLE 130D.  $^1\text{H NMR}$  (500 MHz, pyridine- $d_5$ , 90°C.)  $\delta$  12.40 (s, 1H), 8.52 (s, 1H), 8.43 (s, 1H), 8.20 (m, 2H), 7.95 (bs, 1H), 7.80 (s, 1H), 7.46 (d, 1H), 7.36 (d, 2H), 7.07 (d, 2H), 7.05 (s, 1H), 6.75 (d, 1H), 6.59 (s, 1H), 6.47 (s, 1H), 3.65-3.50 (m, 5H), 3.20 (s, 3H), 3.04 (m, 5H), 2.81 (s, 3H), 2.74 (m, 1H), 2.24 (m, 7H), 2.06 (s, 2H), 2.00 (s, 2H), 1.75 (m, 1H), 1.57 (m, 2H), 1.42 (t, 2H), 1.15 (m, 1H), 0.95 (s, 6H).

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## Example 229

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[1-(cyanomethyl)piperidin-3-yl]methyl}amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

## Example 229A

4-((1-(cyanomethyl)piperidin-3-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 228B for EXAMPLE 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

## Example 229B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[1-(cyanomethyl)piperidin-3-yl]methyl}amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared by substituting EXAMPLE 229A for EXAMPLE 130C in EXAMPLE 130D.  $^1\text{H NMR}$  (500 MHz, pyridine- $d_5$ )  $\delta$  13.06 (s, 1H), 9.03 (s, 1H), 8.42 (s, 1H), 8.30 (d, 1H), 8.10 (d, 1H), 7.68 (m, 2H), 7.44 (d, 2H), 7.08 (m, 3H), 6.99 (d, 1H), 6.75 (d, 1H), 6.51 (m, 2H), 3.78 (m, 2H), 3.43 (d, 1H), 3.13 (m, 1H), 3.04 (m, 4H), 2.76 (s, 2H), 2.71-2.65 (m, 3H), 2.52 (m, 1H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.84 (m, 1H), 1.68 (m, 1H), 1.50 (m, 2H), 1.39 (t, 2H), 1.07-0.99 (m, 1H), 0.93 (s, 6H).

## Example 230

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[1-(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 230A

4-((4-fluoro-1-methylpiperidin-4-yl)methoxy)-3-(trifluoromethylsulfonyl)benzenesulfonamide

To a solution of (4-fluoro-1-methylpiperidin-4-yl)methanol (0.315 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.342 g). After stirring for 15 minutes, 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (0.658 g) was added as a solution in tetrahydrofuran (2 mL) followed by additional tetrahydrofuran (5 mL). After stirring for 1 hour, the reaction was poured in dichloromethane (50 mL) and water (25 mL) and the pH of the water layer was adjusted to 8. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was chromatographed over silica gel (Reveleris 40 g) eluting with a gradient of 1.0% to 10% 7N  $\text{NH}_3$  in methanol/dichloromethane over 20 minutes then maintaining 10% 7N  $\text{NH}_3$  in methanol/dichloromethane for 5 minutes (flow=30 mL/min) to provide the title compound.

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## Example 230B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 230A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63-11.57 (m, 1H), 8.40-8.36 (m, 1H), 8.28-8.17 (m, 1H), 7.97 (s, 1H), 7.53 (d, 1H), 7.50-7.32 (m, 5H), 7.05 (d, 1H), 7.05 (d, 1H), 6.68-6.61 (m, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 4.55-4.40 (m, 2H), 3.06 (s, 8H), 2.79 (s, 4H), 2.06 (d, 13H), 1.39 (s, 2H), 0.93 (s, 6H).

## Example 231

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 231A

(R)-5-chloro-6-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)pyridine-3-sulfonamide

To EXAMPLE 207A (0.051 g) and EXAMPLE 40A (0.049 g) in dioxane (5 mL) was added diisopropylethylamine (0.131 mL) and the reaction was heated to 75° C. for 1 hour then 85° C. for 2 days. The reaction was concentrated, loaded onto silica gel (Reveleris 12 g) and eluted with a gradient of 0.75% methanol/dichloromethane to 7.5% methanol/dichloromethane to provide the title compound.

## Example 231B

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 231A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.44-11.11 (m, 1H), 8.44 (d, 1H), 8.07 (d, 1H), 7.90 (d, 1H), 7.61 (d, 1H), 7.52 (dd, 2H), 7.34 (d, 2H), 7.19 (s, 1H), 7.04 (d, 2H), 6.67 (d, 1H), 6.42 (dd, 1H), 6.16 (s, 1H), 4.77-4.39 (m, 5H), 3.19-2.63 (m, 11H), 2.19 (s, 7H), 1.91 (d, 3H), 1.38 (s, 2H), 0.92 (s, 6H).

## Example 232

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfonyl]-2-nitrophenyl)amino]piperazine-1-carboxylate

## Example 232A

tert-butyl 4-nitrosopiperazine-1-carboxylate

In a 500 mL round-bottomed flask, 6N aqueous HCl (30 mL) was cooled to -10° C., and tert-butyl piperazine-1-car-

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boxylate (10 g) was added. Sodium nitrite (4.5 g) dissolved in 35 mL water was added slowly. NaOH (10 g in 20 mL water) was used to neutralize the solution. Dichloromethane (3×50 mL) was used to extract the product. After drying over Na<sub>2</sub>SO<sub>4</sub> and filtration, the solution was concentrated. The crude product was added to a silica gel column (Analogix, SF65-400 g) and purified by eluting with 0-30% ethyl acetate in hexane.

## Example 232B

tert-butyl 4-aminopiperazine-1-carboxylate

In a 100 mL round-bottomed flask was added EXAMPLE 232A (0.15 g) and zinc (1 g) in water/methanol (1:1, 10 mL) to give a suspension. The mixture was cooled to 0° C. 12N Aqueous HCl (2 mL) was added slowly, and the mixture was stirred at 0° C. for 30 minutes. 2N Aqueous NaOH solution was used to adjust the mixture to basic pH. The mixture was filtered, and extracted with ether (3×30 mL). After drying over Na<sub>2</sub>SO<sub>4</sub>, filtration, and concentration, the crude product was added to a silica gel column (Analogix, SF15-12 g) and purified by eluting with 0-25% ethyl acetate in hexane.

## Example 232C

tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 232B for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 232D

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfonyl]-2-nitrophenyl)amino]piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 232C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.47 (br. s, 1H), 8.86 (s, 1H), 8.34 (d, 1H), 7.90 (d, 1H), 7.59 (m, 2H), 7.36 (m, 4H), 7.23 (m, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.27 (m, 2H), 2.99 (m, 5H), 2.76 (m, 6H), 2.19 (m, 6H), 1.96 (s, 2H), 1.41 (m, 11H), 1.24 (m, 4H), 0.93 (s, 6H).

## Example 233

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro-lambda-6-sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 233A

2-(5-bromo-2-nitrophenyl)sulfur pentafluoride

To a solution of 3-bromophenylsulfur pentafluoride (2.18 g) in concentrated H<sub>2</sub>SO<sub>4</sub> (5 mL) was added KNO<sub>3</sub> (780 mg). The mixture was stirred overnight. The mixture was diluted with diethyl ether (100 mL) and washed with water and brine.

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After drying over Na<sub>2</sub>SO<sub>4</sub> and filtration, the solvent was evaporated under vacuum to provide the title compound.

## Example 233B

## 2-(5-bromo-2-aminophenyl)sulfur pentafluoride

EXAMPLE 233A (6.4 g) and tetrahydrofuran (300 mL) were added to Ra—Ni, (12.80 g) in a 50 mL pressure bottle and the mixture stirred for 2 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and the filtrate was concentrated under vacuum to provide the title compound.

## Example 233C

## 4-bromo-2-pentafluorosulfanyl-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

To a solution of EXAMPLE 233B (4.4 g) in methanol (50 mL) was added tetrahydro-2H-pyran-4-carbaldehyde (1.68 g) and decaborane (1.1 g). The mixture was stirred and monitored by thin layer chromatography. More tetrahydro-2H-pyran-4-carbaldehyde (500 mg) was added to the stirring mixture to drive the reaction to completion. The reaction mixture was concentrated under vacuum and ethyl acetate (500 mL) and brine (200 mL) were added. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent and flash chromatography (20% ethyl acetate in hexane) gave the title compound.

## Example 233D

## 4-thioacetoxyl-2-pentafluorosulfanyl-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

To a solution of EXAMPLE 233C (456 mg) and potassium ethanethioate (197 mg) in dioxane (4 mL) was added tris(dibenzylideneacetone)dipalladium(0) (27 mg) and xantphos (33 mg) followed by N,N-diisopropylethylamine (0.5 mL). The mixture was purged with argon, sealed and stirred under microwave irradiation for 60 minutes at 120° C. The mixture was dissolved in ethyl acetate (300 mL) and water (100 mL). The organic phase was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent followed by flash chromatography (20% ethyl acetate in hexane) provided the title compound.

## Example 233E

## 3-pentafluorosulfanyl-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenylsulfonamide

N-chlorosuccinimide (527 mg) was added to a mixture of 2N aqueous HCl (1.5 mL) and acetonitrile (12 mL) and then cooled to 0° C. A solution of EXAMPLE 233D (386 mg) in acetonitrile (3 mL) was added to the mixture which was then stirred at 0° C. for 2 hours, and then diluted with ethyl acetate (300 mL) and washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of solvent, the residue was dissolved in isopropyl alcohol (20 mL) and cooled to 0° C. with stirring. Then, ammonium hydroxide (conc. 10 mL) was added to mixture. After stirring for 2 hours, the mixture was concentrated under vacuum and the residue was added to ethyl acetate (400 mL) and water (150 mL). The organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration

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and evaporation of solvent, the residue was purified by flash column (20% ethyl acetate in dichloromethane) to provide the title compound.

## Example 233F

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro-lambda-6-sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 233E for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.33 (m, 1H), 8.12 (m, 2H), 7.72 (d, 1H), 7.54 (m, 3H), 7.33 (m, 2H), 7.02 (m, 3H), 6.67 (m, 2H), 6.42 (m, 1H), 6.16 (d, 1H), 3.82 (m, 2H), 3.21 (m, 4H), 3.05 (m, 4H), 2.73 (s, 2H), 2.21 (m, 8H), 1.97 (m, 3H), 1.29 (m, 4H), 0.92 (s, 6H).

## Example 234

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 234A

## 4-vinyltetrahydro-2H-pyran-4-ol

Dihydro-2H-pyran-4(3H)-one (8.01 g) in anhydrous ethyl ether (50 mL) was treated with 1.0 M vinylmagnesium bromide (104 mL) over 20 minutes at 0° C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH<sub>4</sub>Cl, and the organic layer was separated. The aqueous layer was extracted with additional ethyl ether three times. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 20% ethyl acetate in hexanes to provide the title compound.

## Example 234B

## 4-methoxy-4-vinyltetrahydro-2H-pyran

To a solution of EXAMPLE 234A (9.4 g) in tetrahydrofuran (150 mL) was added 60% sodium hydride (5.28 g) at 0° C. portionwise. After the addition was complete, the solution was heated under reflux for three hours. After cooling, to this suspension was added dimethyl sulfate (8.41 mL) slowly. The solution was heated under reflux overnight, cooled to room temperature, and hydrolyzed with cool saturated aqueous NH<sub>4</sub>Cl. After extraction with diethyl ether several times, the combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 1-10% ethyl acetate in hexanes to provide the title compound.

## Example 234C

## 4-methoxytetrahydro-2H-pyran-4-carbaldehyde

EXAMPLE 234B (4.3 g) in tetrahydrofuran (200 mL) and water (67 mL) was treated with 4% osmium tetroxide in water

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(9.24 mL). To this solution was added potassium periodate (13.91 g) portionwise over 2 hours. The solution was stirred overnight at room temperature. Water was added to the mixture followed by repeat extractions with diethyl ether. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 5-20% ethyl acetate in hexanes to provide the title compound.

## Example 234D

(4-methoxytetrahydro-2H-pyran-4-yl)methanol

EXAMPLE 234C (1.8 g) in 2-propanol (28 mL) and water (7 mL) was cooled to 0° C. To this solution was added sodium borohydride (0.709 g). The solution was stirred and allowed to warm to room temperature over 3 hours. The reaction was quenched with acetone, and stirred for another 1 hour. The clear liquid was separated from solid by decanting. Additional ethyl acetate was used to wash the solid, and was the mixture was decanted. The combined organic solutions were concentrated. The residue was purified by flash chromatography on silica gel eluting 1:1 ethyl acetate:hexane to provide the title compound.

## Example 234E

4-((4-methoxytetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 234D for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 234F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 234E for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.36 (s, 1H), 8.04-8.07 (m, 2H), 7.50-7.53 (m, 3H), 7.45 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.21 (s, 2H), 3.65-3.67 (m, 2H), 3.53-3.56 (m, 2H), 3.19 (s, 3H), 3.10 (s, 4H), 2.86 (s, 2H), 2.30 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.61-1.74 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 235

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 235A

(R)-tert-butyl 3-(2-nitro-4-sulfamoylphenoxy)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-hydroxypyrrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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## Example 235B

(R)-tert-butyl 3-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenoxy)pyrrolidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 235A for EXAMPLE 1F in EXAMPLE 1G.

## Example 235C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 235B (0.230 g) in dichloromethane (3 mL) was added trifluoroacetic acid (0.377 mL). After stirring for 4 hours, the reaction was concentrated then dissolved in dichloromethane (3 mL) and treated with 1,3-difluoropropan-2-one (0.028 g) followed by sodium triacetoxyborohydride (0.078 g). After stirring for 4 hours, the reaction was quenched by the addition of saturated aqueous NaHCO<sub>3</sub> and dichloromethane (5 mL). The reaction was diluted with dichloromethane (250 mL) and saturated aqueous NaHCO<sub>3</sub> (100 mL) was added. The organic layer was separated, washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated. Trituration with acetonitrile gave the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.34 (s, 1H), 8.03 (s, 2H), 7.52 (d, 3H), 7.35 (d, 3H), 7.04 (d, 2H), 6.75-6.60 (m, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 5.17-5.06 (m, 1H), 4.60 (d, 4H), 2.98 (d, 12H), 2.37-2.02 (m, 6H), 1.96 (s, 3H), 1.39 (s, 2H), 0.93 (s, 6H).

## Example 236

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 236A

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperazin-1-ylamino)phenyl)sulfonylbenzamide

The title compound was prepared by substituting EXAMPLE 232D for EXAMPLE 1A in EXAMPLE 1B.

## Example 236B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 236A for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (br. s, 1H), 9.20 (s, 1H), 8.53 (d, 1H), 8.04 (d, 1H),



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7.83 (dd, 1H), 7.53 (m, 4H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.18 (d, 1H), 4.55 (t, 2H), 4.44 (t, 2H), 3.47 (m, 1H), 3.06 (m, 4H), 2.88 (m, 4H), 2.74 (m, 4H), 2.09 (m, 11H), 1.38 (t, 2H), 0.91 (s, 6H).

## Example 237

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 236A for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (br. s, 1H), 9.27 (d, 1H), 9.23 (s, 1H), 8.44 (m, 2H), 8.12 (d, 1H), 7.68 (m, 3H), 7.44 (m, 2H), 7.06 (m, 2H), 6.75 (dd, 1H), 6.51 (m, 2H), 4.02 (m, 2H), 3.31 (m, 2H), 3.06 (m, 4H), 2.91 (m, 5H), 2.76 (s, 2H), 2.38 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.65 (m, 2H), 1.39 (m, 7H), 0.93 (s, 6H).

## Example 238

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{(3R)-tetrahydrofuran-3-ylamino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 238A

(R)-3-nitro-4-(tetrahydrofuran-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting (R)-tetrahydrofuran-3-amine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 238B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{(3R)-tetrahydrofuran-3-ylamino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 238A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.47 (d, 1H), 8.19 (m, 2H), 7.97 (d, 1H), 7.74 (m, 1H), 7.52 (d, 1H), 7.46 (t, 1H), 7.34 (m, 2H), 7.05 (m, 2H), 6.96 (d, 1H), 6.89 (d, 1H), 6.65 (dd, 1H), 6.33 (m, 1H), 6.22 (d, 1H), 4.31 (m, 1H), 3.92 (m, 1H), 3.87 (m, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.04 (m, 4H), 2.73 (m, 2H), 2.33 (m, 1H), 2.18 (m, 6H), 1.95 (m, 2H), 1.88 (m, 1H), 1.39 (t, 2H), 0.92 (s, 6H).

## Example 239

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 239A

tert-butyl (4,4-difluorocyclohexyl)methylcarbamate

Tert-butyl (4-oxocyclohexyl)methylcarbamate (5 g) and diethylaminosulfur trifluoride (7.45 g) were stirred in dichlo-

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romethane (100 mL) for 24 hours. The mixture was quenched with pH 7 buffer (100 mL), and poured into ether (400 mL). The resulting solution was separated, and the organic layer was washed twice with water, and once with brine, and then concentrated to give the crude product and fluoroolefin by-product in a 3:2 ratio. The crude material was taken up in tetrahydrofuran (70 mL) and water (30 mL), and N-methylmorpholine-N-oxide (1.75 g), and OsO<sub>4</sub> (2.5 wt % solution in t-butanol) were added, and the mixture was stirred for 24 hours. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was then added, and the mixture was stirred for 30 minutes. The mixture was then diluted with ether (300 mL), and the resulting solution was separated, and rinsed twice with water, and once with brine, and concentrated. The crude product was chromatographed on silica gel using 5-10% ethyl acetate in hexanes to provide the title compound.

## Example 239B

(4,4-difluorocyclohexyl)methanamine

A solution of EXAMPLE 239A (3 g) in dichloromethane (35 mL), trifluoroacetic acid (15 mL), and triethylsilane (1 mL) was stirred for 2 hours. The solution was concentrated, then concentrated from toluene, and left on high vacuum for 24 hours. The semi-solid was taken up in ether/hexane and filtered to provide the title compound as its trifluoroacetic acid salt.

## Example 239C

4-((4,4-difluorocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 239B for (tetrahydropyran-4-yl)methanamine in EXAMPLE 1F.

## Example 239D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 239C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 12.40 (s, 1H), 11.61 (br s, 1H), 8.53 (m, 1H), 8.50 (d, 1H), 7.99 (d, 1H), 7.73 (d, 1H), 7.49 (m, 2H), 7.32 (d, 2H), 7.04 (d, 2H), 7.00 (d, 1H), 6.65 (d, 1H), 6.32 (s, 1H), 6.21 (s, 1H), 3.37 (m, 4H), 3.06 (m, 4H), 2.73 (m, 2H), 2.18 (m, 4H), 1.97 (m, 4H), 1.81 (m, 4H), 1.38 (m, 2H), 1.20 (m, 4H), 0.92 (s, 6H).

## Example 240

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 240A

4-(1-tert-butylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

To a mixture of 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (307 mg) and EXAMPLE 227A (156 mg)

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in tetrahydrofuran (4 mL) was added Hunig's Base (1 mL). The mixture was stirred for 3 days. The mixture was diluted with ethyl acetate (300 mL) and water (100 mL) and stirred until the solid disappeared into the solution. The layers were separated and the organic phase was washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the combined aqueous layers were extracted again with ethyl acetate and the combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was evaporated to provide the title compound.

## Example 240B

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 240A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.53 (s, 1H), 8.04 (s, 1H), 7.94 (d, 1H), 7.86 (m, 1H), 7.55 (d, 2H), 7.44 (d, 1H), 7.33 (m, 3H), 7.05 (d, 2H), 6.92 (m, 1H), 6.62 (dd, 1H), 6.43 (m, 1H), 6.29 (d, 2H), 3.79 (m, 1H), 3.05 (m, 6H), 2.73 (s, 3H), 2.19 (m, 8H), 1.96 (s, 3H), 1.27 (m, 12H), 0.92 (s, 6H).

## Example 241

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 241A

tert-butyl 2-((4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydro-pyran-4-yl)methylamine and 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 1F.

## Example 241B

tert-butyl 2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 241A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.

## Example 241C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-(morpholin-2-ylmethylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 241B for EXAMPLE 1A in EXAMPLE 1B.

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## Example 241D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 241C for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.15 (d, 1H), 8.04 (d, 1H), 7.92 (dd, 1H), 7.54 (d, 1H), 7.51 (t, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.25 (m, 1H), 7.04 (m, 3H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.19 (d, 1H), 4.54 (t, 2H), 4.43 (m, 2H), 3.85 (m, 1H), 3.69 (m, 1H), 3.52 (m, 1H), 3.48 (m, 1H), 3.39 (m, 2H), 3.07 (m, 4H), 2.77 (br s, 2H), 2.69 (d, 1H), 2.56 (d, 1H), 2.21 (br s, 4H), 2.15 (t, 2H), 1.94 (m, 3H), 1.76 (t, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 242

N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 242A

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 138D.

## Example 242B

N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 242A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 8.41 (d, 1H), 8.07 (d, 1H), 7.93 (d, 1H), 7.60 (d, 1H), 7.51-7.53 (m, 2H), 7.40 (s, 1H), 7.33-7.35 (m, 2H), 7.03-7.05 (m, 2H), 6.68 (dd, 1H), 6.42 (dd, 1H), 6.16 (d, 1H), 3.77 (d, 1H), 3.69-3.71 (m, 3H), 3.48-3.53 (m, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.14-2.20 (m, 6H), 1.96 (s, 2H), 1.65-1.76 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

## Example 243

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 243A

5-chloro-6-(1-cyclopropylpiperidin-4-ylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-chloro-3-nitrobenzenesulfonamide,

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1-cyclopropylpiperidin-4-amine for 4-methylpiperazin-1-amine dihydrochloride and Hunig's base for N<sup>1</sup>,N<sup>1</sup>,N<sup>2</sup>,N<sup>2</sup>-tetramethylethane-1,2-diamine in EXAMPLE 6A.

**Example 243B**

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 243A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.40 (d, 1H), 8.05 (d, 1H), 7.88 (d, 1H), 7.56 (d, 1H), 7.50 (m, 2H), 7.34 (d, 2H), 7.03 (d, 2H), 6.97 (br d, 1H), 6.66 (dd, 1H), 6.40 (m, 1H), 6.16 (d, 1H), 4.04 (m, 1H), 3.03 (br m, 6H), 2.73 (s, 2H), 2.42 (br m, 2H), 2.18 (br m, 6H), 1.95 (s, 2H), 1.80 (m, 3H), 1.62 (m, 2H), 1.38 (t, 2H), 0.91 (s, 6H), 0.47 (m, 2H), 0.40 (br m, 2H).

**Example 244**

N-[(5-chloro-6-[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 244A**

(S)-tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

**Example 244B**

(S)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244A for EXAMPLE 113A in EXAMPLE 134A.

**Example 244C**

(S)-5-chloro-6-((4-(cyanomethyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

**Example 244D**

N-[(5-chloro-6-[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 244C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.99 (s, 1H), 9.09 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.55 (dd, 1H), 4.43 (dd, 1H), 4.05 (m, 1H), 3.85 (d, 1H), 3.76 (s, 2H), 3.63 (dt, 1H), 3.06 (m, 4H), 2.91 (d, 1H), 2.77 (s, 2H), 2.58 (d, 1H), 2.51-2.44 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 245**

N-[(5-chloro-6-[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 245A**

(S)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

**Example 245B**

N-[(5-chloro-6-[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 245A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.09 (d, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.11 (t, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (s, 1H), 6.54 (s, 1H), 6.49 (s, 1H), 4.85-4.46 (m, 3H), 4.45-3.87 (m, 3H), 3.50 (m, 1H), 3.37 (dd, 1H), 3.21 (m, 2H), 3.07 (m, 4H), 2.86 (t, 1H), 2.77 (s, 2H), 2.27 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 246**

N-[(5-chloro-6-[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 246A**

(R)-tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

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## Example 246B

(R)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 246A for EXAMPLE 113A in EXAMPLE 134A.

## Example 246C

(R)-5-chloro-6-((4-(cyanomethyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 246B for EXAMPLE 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

## Example 246D

N-[(5-chloro-6-[[2-(4-(cyanomethyl)morpholin-2-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 246C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.99 (s, 1H), 9.09 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.55 (dd, 1H), 4.43 (dd, 1H), 4.05 (m, 1H), 3.85 (d, 1H), 3.76 (s, 2H), 3.63 (dt, 1H), 3.06 (m, 4H), 2.91 (d, 1H), 2.77 (s, 2H), 2.58 (d, 1H), 2.51-2.44 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 247

N-[(5-chloro-6-[[2-(4-(N,N-dimethylglycyl)morpholin-2-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 247A

(R)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 246B for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

## Example 247B

N-[(5-chloro-6-[[2-(4-(N,N-dimethylglycyl)morpholin-2-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 247A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.09 (d, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.11 (t, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (s, 1H), 6.54 (s, 1H), 6.49 (s,

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1H), 4.85-4.46 (m, 3H), 4.45-3.87 (m, 3H), 3.50 (m, 1H), 3.37 (dd, 1H), 3.21 (m, 2H), 3.07 (m, 4H), 2.86 (t, 1H), 2.77 (s, 2H), 2.27 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 248

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-((5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 248A

5-bromo-3-fluoro-2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine

The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 248B

tert-butyl 5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

EXAMPLE 248A (0.308 g), tert-butyl carbamate (0.141 g), palladium(II) acetate (0.011 g), Xantphos (0.043 g) and cesium carbonate (0.489 g) were combined with dioxane (5.0 mL) in a 20-mL vial equipped with a magnetic stir bar. The vial was flushed with nitrogen, capped and stirred at 100° C. overnight. Additional palladium(II) acetate (0.011 g), Xantphos (0.043 g) and tert-butyl carbamate (0.141 g) were added and heating was continued at 100° C. for 8 hours. The cooled reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on silica gel with 7-25% ethyl acetate in hexanes as the eluent.

## Example 248C

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

Under ice-cooling, thionyl chloride (1.563 mL) was added dropwise over 20 minutes to water (9 mL). The mixture was stirred for 12 hours to give a SO<sub>2</sub>-containing solution. Separately, EXAMPLE 248B (0.295 g) was added to a mixture of 1,4-dioxane (3.2 mL) and concentrated HCl (8 mL) at 0° C. After stirring for 15 minutes, a solution of sodium nitrite (0.065 g) in water (2 mL) was added dropwise and stirring was continued at 0° C. for 3 hours. Copper(I) chloride (0.042 g) and then the freshly prepared solution of diazotized material were added sequentially to the previously prepared SO<sub>2</sub>-containing solution. The resulting solution was stirred for 30 minutes and then extracted with ethyl acetate (2×125 mL). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on silica gel with 5% ethyl acetate in hexanes as the eluent.

## Example 248D

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 248C (0.08 g) in isopropanol (2 mL) at 0° C. was treated with ammonium hydroxide (1.697 mL), stirred



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overnight and then concentrated to dryness. The obtained solid was slurried in water, filtered, rinsed with water and dried under high vacuum to provide the title compound.

## Example 248E

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 248D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.03 (d, 1H), 8.44 (dd, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.67 (m, 1H), 7.65 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.77 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.55 (d, 2H), 3.80 (m, 4H), 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.88 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 250

N-([5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 250A

5-chloro-6-((3-methyloxetan-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting (3-methyloxetan-3-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 250B

N-([5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 250A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.22 (d, 1H), 8.51 (d, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.66 (t, 2H), 7.43-7.46 (m, 2H), 7.04-7.09 (m, 2H), 6.75 (dd, 1H), 6.45-6.54 (m, 2H), 4.47 (s, 2H), 3.81-3.84 (m, 2H), 3.74 (d, 2H), 3.03-3.11 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10-2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.16 (s, 3H), 0.94 (s, 6H).

## Example 251

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 251A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting (4-fluorotetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-

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pyran-4-yl)methanol and 5-bromo-6-chloropyridine-3-sulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 251B

6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

To a suspension of 5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide (200 mg) and cyclohexene (0.549 mL) in ethyl acetate (10 mL) was added 10% palladium on carbon (57.6 mg). The suspension was stirred for 60 minutes at 120° C. The reaction mixture was filtered and concentrated. The product was purified by reverse-phase flash chromatography (C18, 150 g, 10%-100% acetonitrile/H<sub>2</sub>O/trifluoroacetic acid 0.1%).

## Example 251C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 251B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.29 (d, 1H), 8.50 (dd, 1H), 8.41 (d, 1H), 8.07 (d, 1H), 7.66-7.70 (m, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.84 (d, 1H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.50 (d, 2H), 3.81-3.89 (m, 2H), 3.70-3.81 (m, 2H), 3.02-3.12 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10-2.18 (m, 4H), 1.97 (s, 2H), 1.77-1.94 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 252

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1,3-difluoropropan-2-yl)morpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 252A

tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and tert-butyl morpholin-2-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 252B

(4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methanamine

A solution of EXAMPLE 252A (538 mg) in dioxane (4 mL) was treated with 4.0M HCl in dioxane solution (1.8 mL).

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The reaction was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and used without further purification.

## Example 252C

4-((4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 252B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 252D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 252C for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.59 (t, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.51 (m, 3H), 7.33 (d, 2H), 7.07 (d, 1H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.69 (t, 2H), 4.57 (t, 2H), 3.85 (m, 1H), 3.70 (m, 1H), 3.52 (m, 2H), 3.41 (m, 2H), 3.07 (br s, 4H), 2.91 (d, 1H), 2.74 (m, 3H), 2.59 (m, 1H), 2.43 (m, 1H), 2.20 (m, 4H), 2.15 (m, 2H), 1.95 (br s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

## Example 253

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 253A

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate for tetrahydro-2H-pyran-4-ylmethanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 253B

5-chloro-6-(piperidin-4-ylmethoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

The title compound was prepared by substituting EXAMPLE 253A for EXAMPLE 39A in EXAMPLE 39B.

## Example 253C

5-chloro-6-((1-(cyanomethyl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 253B (0.061 g), 2-chloroacetonitrile (0.017 g), sodium carbonate (0.025 g) and N,N-dimethylformamide (1 mL) were combined in a 4-mL vial and heated at 60° C. overnight. The cooled reaction mixture was diluted with ethyl

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acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on silica gel with 2-10% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 253D

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 253C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 9.14 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (t, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.74 (dd, 1H), 6.50 (m, 2H), 4.18 (d, 2H), 3.64 (s, 2H), 3.05 (s, 4H), 2.77 (m, 4H), 2.24 (m, 4H), 2.13 (m, 4H), 1.97 (s, 2H), 1.69 (m, 3H), 1.41 (m, 4H), 0.93 (s, 6H).

## Example 254

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 254A

(R)-tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 254B

(R)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 254A for EXAMPLE 113A in EXAMPLE 134A.

## Example 254C

(R)-4-(1-(2-(2-methoxyethoxy)ethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

To a solution of (R)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesulfonamide (440 mg) in N,N-dimethylformamide (10 mL) was added sodium carbonate (132 mg) and 1-bromo-2-(2-methoxyethoxy)ethane (0.155 mL). The reaction mixture was heated at 60° C. for 18 hours and after an aqueous workup, the crude product was purified on silica gel with a 2.5-10% methanol in methylene chloride gradient to provide the title compound.

## Example 254D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yl-oxy)benzamide

The title compound was prepared by substituting EXAMPLE 254C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.96 (m, 1H), 9.25 (m, 1H), 8.57 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.76 (dd, 1H), 6.55 (m, 1H), 6.47 (m, 1H), 5.26 (br s, 1H), 4.02 (m, 1H), 3.63 (m, 4H), 3.53 (m, 2H), 3.28 (s, 3H), 3.07 (m, 4H), 2.89-2.81 (m, 2H), 2.78 (s, 2H), 2.75-2.66 (m, 3H), 2.37 (m, 1H), 2.26 (m, 2H), 2.24-2.18 (m, 1H), 2.15 (m, 4H), 1.97 (s, 2H), 1.65 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 255

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 255A

(R)-4-(1-(2-(dimethylamino)acetyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride, hydrochloric acid for 1-bromo-2-(2-methoxyethoxy)ethane in EXAMPLE 254C except the reaction was stirred at ambient temperature for 18 hours.

## Example 255B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 255A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.01 (d, 1H), 9.26 (m, 1H), 8.46-8.33 (m, 3H), 8.14 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.01-6.89 (m, 1H), 6.76 (dd, 1H), 6.55 (m, 1H), 6.48 (m, 1H), 5.32 (br s, 1H), 4.27-4.14 (m, 1H), 4.05-3.95 (m, 1H), 3.82-3.62 (m, 3H), 3.27-3.15 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.34 (2, 3H), 2.32 (s, 3H), 2.30-2.20 (m, 3H), 2.15 (m, 4H), 1.97 (s, 2H), 1.87-1.81 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 256

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 256A

tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)azetidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 3-aminoazetidine-1-carboxylate for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

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## Example 256B

4-(azetidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 256A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

## Example 256C

3-nitro-4-(1-(oxetan-3-yl)azetidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 256B for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 256D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 256C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 9.27 (d, 1H), 8.62 (d, 1H), 8.42 (d, 1H), 8.35 (dd, 1H), 8.09 (d, 1H), 7.67 (m, 1H), 7.63 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.67 (d, 1H), 6.55 (d, 1H), 6.48 (dd, 1H), 4.66 (t, 2H), 4.58 (m, 2H), 4.23 (m, 1H), 3.71 (m, 3H), 3.12 (dd, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (t, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 257

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 257A

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 126A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 257B

5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

The title compound was prepared by substituting EXAMPLE 257A for EXAMPLE 39A in EXAMPLE 39B.

## Example 257C

5-chloro-6-((1-(cyanomethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.166 g) in acetonitrile (3 mL) was treated with 2-chloroacetonitrile (0.027 g) and sodium car-

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bonate (0.064 g), heated at 60° C. overnight, cooled to room temperature and chromatographed on silica gel with 0 to 3% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent. The obtained solid was slurried in water, filtered, rinsed with water and diethyl ether, and dried in a vacuum oven at 80° C.

## Example 257D

N-[(5-chloro-6-[[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 257C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.12 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 4.49 (d, 2H), 3.72 (s, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.73 (m, 4H), 2.26 (t, 2H), 2.13 (m, 4H), 2.07 (m, 2H), 1.90 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 258

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-((2R)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 258A

(S)-tert-butyl  
2-(tosyloxymethyl)morpholine-4-carboxylate

To a solution of (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (1 g) in dichloromethane (50 mL) was added triethylamine (1.604 mL) and 4-methylbenzene-1-sulfonyl chloride (1.097 g). The mixture was stirred at ambient temperature under nitrogen for 72 hours. The reaction was diluted with methylene chloride (50 mL) and brine (100 mL). The brine layer was extracted with methylene chloride (75 mL). The combined organics were dried over sodium sulfate, filtered and concentrated. The crude material was purified on a silica gel column eluting with a 15-65% ethyl acetate in hexane gradient to provide the title compound.

## Example 258B

(S)-tert-butyl  
2-(azidomethyl)morpholine-4-carboxylate

A solution of EXAMPLE 258A (1.66 g) and sodium azide (0.581 g) in anhydrous N,N-dimethylformamide (10 mL) was stirred at 90° C. for 4 hours. The mixture was cooled and concentrated to dryness. The residue was taken up in 5% aqueous sodium carbonate solution and extracted with methylene chloride. The organic solution was dried (MgSO<sub>4</sub>), filtered and concentrated to give a solid.

## Example 258C

(R)-tert-butyl  
2-(aminomethyl)morpholine-4-carboxylate

This compound was obtained by hydrogenation of EXAMPLE 258B under 60 psi of hydrogen over 10% palla-

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dium on carbon in methanol for 24 hours, followed by filtration and evaporation of the solvent.

## Example 258D

(R)-tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 258C for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 258E

(S)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258D for EXAMPLE 113A in EXAMPLE 134A.

## Example 258F

(R)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258E for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

## Example 258G

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-((2R)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 258F for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 259

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-((2S)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 259A

(R)-tert-butyl  
2-(tosyloxymethyl)morpholine-4-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate in EXAMPLE 258A.



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## Example 259B

(R)-tert-butyl  
2-(azidomethyl)morpholine-4-carboxylate

The title compound was prepared by substituting  
EXAMPLE 259A for EXAMPLE 258A in EXAMPLE  
258B.

## Example 259C

(S)-tert-butyl  
2-(aminomethyl)morpholine-4-carboxylate

The title compound was prepared by substituting  
EXAMPLE 259B for EXAMPLE 258B in EXAMPLE 258C.

## Example 259D

(S)-tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)  
methyl)morpholine-4-carboxylate

The title compound was prepared by substituting  
EXAMPLE 259C for (tetrahydropyran-4-yl)methylamine in  
EXAMPLE 1F.

## Example 259E

(R)-4-(morpholin-2-ylmethylamino)-3-nitrobenzene-  
sulfonamide

The title compound was prepared by substituting  
EXAMPLE 259D for EXAMPLE 113A in EXAMPLE  
134A.

## Example 259F

(S)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)  
methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting  
EXAMPLE 259E for EXAMPLE 134A and 2-(dimethyl-  
amino)acetyl chloride hydrochloride for methyl iodide in  
EXAMPLE 134B.

## Example 259G

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl)piperazin-1-yl)-N-([4-([[(2S)-4-(N,  
N-dimethylglycyl)morpholin-2-yl]methyl]amino)-3-  
nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 259F for EXAMPLE 130C in EXAMPLE 130D.  
<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.27 (d,  
1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H),  
7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75  
(d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd,  
1H), 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd, 1H),

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3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H),  
2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t,  
2H), 0.94 (s, 6H).

## Example 260

N-[(5-chloro-6-([1-(N,N-dimethylglycyl)piperidin-  
4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-([2-(4-  
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]  
methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

## Example 260A

5-chloro-6-((1-(2-(dimethylamino)acetyl)piperidin-  
4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 253B (0.061 g), 2-(dimethylamino)acetyl  
chloride, hydrochloric acid (0.061 g), and sodium carbonate  
(0.032 g) were combined in a 4-mL vial with N,N-dimethyl-  
formamide (2 mL). The mixture was stirred at ambient tem-  
perature for 3 days. Additional 2-(dimethylamino)acetyl  
chloride, hydrochloric acid (0.037 g), sodium carbonate  
(0.032 g) and N,N-dimethylformamide (1 mL) were added  
and stirring was continued for 24 hours. The reaction mixture  
was diluted with ethyl acetate, washed with water and brine,  
dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed  
on silica gel with 0 to 20% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 260B

N-[(5-chloro-6-([1-(N,N-dimethylglycyl)piperidin-  
4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-([2-(4-  
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]  
methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 260A for EXAMPLE 11B in EXAMPLE 11D.  
<sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 12.91 (s, 1H), 9.16 (d,  
1H), 8.75 (d, 1H), 8.51 (d, 1H), 8.33 (d, 1H), 7.70 (d, 1H),  
7.62 (d, 1H), 7.45 (m, 2H), 7.09 (m, 2H), 6.77 (dd, 1H), 6.60  
(d, 1H), 6.45 (d, 1H), 4.81 (d, 1H), 4.15 (m, 3H), 3.24 (m, 2H),  
3.04 (m, 4H), 2.89 (m, 1H), 2.79 (s, 2H), 2.53 (m, 1H), 2.29  
(m, 6H), 2.26 (m, 2H), 2.18 (m, 4H), 1.98 (m, 2H), 1.91 (m,  
1H), 1.71 (m, 2H), 1.39 (t, 2H), 1.25 (m, 2H), 0.94 (s, 6H).

## Example 261

N-[(5-chloro-6-([(3R)-1-(2,2-difluoroethyl)pyrroli-  
din-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-([2-(4-  
chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]  
methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

## Example 261A

(R)-tert-Butyl 3-(3-chloro-5-sulfamoylpyridin-2-  
yloxy)pyrrolidine-1-carboxylate

The title compound was prepared by substituting  
EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide

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and (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

**Example 261B**

(R)-5-Chloro-6-(pyrrolidin-3-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 261A for tert-butyl 4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

**Example 261C**

(R)-5-chloro-6-(1-(2,2-difluoroethyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 261B (353 mg), 1,1-difluoro-2-iodoethane (268 mg), sodium carbonate (283 mg) in N,N-dimethylformamide (10 mL) was heated at 80° C. overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel column and eluted using a gradient of 0.5 to 3% methanol in dichloromethane to provide the title compound.

**Example 261D**

N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 261C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.55 (s, 1H), 8.04 (s, 1H), 7.95 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.35 (m, 3H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.24 (d, 1H), 6.25-5.97 (m, 1H), 5.39 (m, 1H), 2.98 (m, 6H), 2.86 (m, 6H), 2.55 (m, 2H), 2.24 (m, 7H), 1.96 (s, 2H), 1.83 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 262**

4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 262A**

(R)-4-(1-(cyanomethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-bromoacetonitrile for 1-bromo-2-(2-methoxyethoxy)ethane in EXAMPLE 254C.

**Example 262B**

4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 262A for EXAMPLE 130C in EXAMPLE

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130D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.53 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.10 (d, 1H), 7.67-7.64 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.81 (d, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 5.15 (br s, 1H), 4.10 (m, 1H), 3.89 (s, 2H), 3.07 (m, 4H), 2.93-2.86 (m, 2H), 2.80-2.77 (m, 3H), 2.61-2.53 (m, 1H), 2.31-2.21 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.75-1.68 (m, 1H), 1.39 (t, 2H), 0.94 (m, 6H).

**Example 263**

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 263A**

tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate

Sodium hydride (6.63 g, 60% in mineral oil) was added to trimethylsulfoxonium iodide (36.5 g) in dimethyl sulfoxide (150 mL) and tetrahydrofuran (150 mL), was and stirred for 30 minutes. tert-Butyl 4-oxopiperidine-1-carboxylate (25.4 g) was added and the reaction was stirred for 3 hours. The reaction was poured into water (800 mL) and extracted three times with ether. The combined extracts were washed three times with water, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to yield the crude product which was used without further purification.

**Example 263B**

tert-butyl 4-(2-(benzyloxy)benzyl)-4-hydroxypiperidine-1-carboxylate

(2-(Benzyloxy)phenyl)magnesium bromide (33.8 mL, 1M) was added to a solution of EXAMPLE 263A (6.0 g) and CuI (1.07 g) in tetrahydrofuran (220 mL) at 0° C. over 10 minutes. The reaction was quenched with pH 7 buffer (20 mL), extracted twice with ether, and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 2-20% ethyl acetate in hexanes to provide the title compound.

**Example 263C**

tert-butyl 4-hydroxy-4-(2-(hydroxybenzyl)piperidine-1-carboxylate

EXAMPLE 263B (11.5 g) and methanol (120 mL) were added to Raney Nickel (1.150 g) in a 250 mL SS pressure bottle and stirred for 1 hour at 30 psi under hydrogen. The mixture was filtered through a nylon membrane and the solution was concentrated to yield the title compound.

**Example 263D**

tert-butyl 4-hydroxy-4-(2-(trifluoromethylsulfonyloxy)benzyl)piperidine-1-carboxylate

A mixture of EXAMPLE 263C (4.6 g), N-phenylbis(trifluoromethanesulfonimide) (5.88 g), and Hunig's base (2.88 mL) in dichloromethane (100 mL) was stirred for 24 hours.

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The mixture was concentrated and chromatographed on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

## Example 263E

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-hydroxypiperidine-1-carboxylate

A mixture of EXAMPLE 263D (4.3 g), 4-chlorophenylboronic acid (1.84 g),  $K_3PO_4$  (2.91 g), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.36 g) in 2-methyltetrahydrofuran (50 mL) was stirred at 70° C. for 24 hours. The reaction was cooled and quenched with water (50 mL), extracted twice with ether, and the combined extracts were washed with brine, dried over  $Na_2SO_4$ , filtered, and concentrated. The crude product was chromatographed on silica gel using 5-30% ethyl acetate in hexanes to provide the title compound.

## Example 263F

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidine-1-carboxylate

Sodium hydride (0.36 g, 60% in mineral oil) was added to EXAMPLE 263E (4.3 g), in tetrahydrofuran (40 mL) and the reaction was stirred for 10 minutes. Hexamethylphosphoramide (5 mL) and  $CH_3I$  (2.34 mL) were added and the reaction was stirred at 50° C. for 18 hours. The reaction was cooled and quenched with water (50 mL), extracted twice with ether, and the combined extracts were washed with brine, dried over  $Na_2SO_4$ , filtered, and concentrated. The crude product was chromatographed on silica gel using 5-25% ethyl acetate in hexanes to provide the title compound.

## Example 263G

4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidine

The title compound was prepared by substituting EXAMPLE 263F for EXAMPLE 1A in EXAMPLE 1B.

## Example 263H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoate

A solution of EXAMPLE 263G (1.4 g), EXAMPLE 3H (1.06 g) and Hunig's base (0.75 mL) in dimethylsulfoxide (20 mL) was stirred at 120° C. for 18 hours. The reaction was cooled and quenched with water (200 mL), extracted three times with ether, and the combined extracts were washed three times with water, and brine, dried over  $Na_2SO_4$ , filtered, and concentrated. The crude product was chromatographed on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

## Example 263I

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 263H for EXAMPLE 3I in EXAMPLE 3J.

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## Example 263J

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 263I for EXAMPLE 1E and EXAMPLE 96A for EXAMPLE 1F in EXAMPLE 1G.  $^1H$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.71 (s, 1H), 11.58 (br s, 1H), 8.58 (d, 1H), 8.28 (d, 1H), 8.05 (d, 1H), 7.56 (d, 1H), 7.52 (m, 1H), 7.46 (d, 1H), 7.44 (d, 2H), 7.28 (m, 5H), 7.11 (dd, 1H), 6.62 (dd, 1H), 6.41 (dd, 1H), 6.11 (d, 1H), 4.54 (d, 2H), 3.75 (m, 2H), 3.59 (m, 2H), 3.20 (m, 2H), 2.97 (s, 3H), 2.81 (m, 2H), 2.74 (m, 2H), 1.89 (m, 2H), 1.83 (m, 2H), 1.36 (m, 2H), 1.09 (m, 2H).

## Example 264

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 263I for EXAMPLE 1E in EXAMPLE 1G.  $^1H$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.71 (s, 1H), 11.40 (br s, 1H), 8.62 (t, 1H), 8.58 (d, 1H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.54 (m, 2H), 7.44 (m, 3H), 7.28 (m, 5H), 7.13 (dd, 1H), 6.62 (dd, 1H), 6.41 (dd, 1H), 6.11 (d, 1H), 3.85 (dd, 2H), 3.31 (m, 4H), 3.20 (m, 2H), 2.97 (s, 3H), 2.81 (m, 2H), 2.73 (m, 2H), 1.89 (m, 1H), 1.62 (m, 2H), 1.38 (m, 2H), 1.25 (m, 2H), 1.09 (m, 2H).

## Example 265

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 265A

benzyl 4-(piperidin-1-ylmethylene)piperidine-1-carboxylate

To a solution of benzyl 4-formylpiperidine-1-carboxylate (12.5 g) in toluene (120 mL) was added piperidine (6.46 g). The mixture was stirred at reflux under a Dean-Stark trap overnight. The mixture was then concentrated under vacuum and the residue was used directly in the next step.

## Example 265B

benzyl  
9-oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylate

To a solution of EXAMPLE 265A (15.88 g) in ethanol (300 mL) was added but-3-enone (3.89 g). The mixture was stirred at reflux overnight. Then acetic acid (30 mL) was added to the mixture which was stirred at reflux again overnight. The mixture was then concentrated under vacuum and the residue was diluted with ethyl acetate (400 mL) and washed with

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water and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, column purification gave the title compound.

## Example 265C

## benzyl

## 9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate

EXAMPLE 265B (21 g) and tetrahydrofuran (160 mL) were added to 5% Pt-C wet (3.15 g) in a 250 mL pressure bottle and stirred for 1 hour at 30 psi and room temperature. The mixture was filtered through a nylon membrane and the filtrate was concentrated under vacuum to provide the title compound.

## Example 265D

## benzyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate

To a solution of EXAMPLE 265C (8.0 g) in dichloromethane (200 mL) was added Dess-Martin Periodinane (11.2 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with 2N aqueous NaOH, water, and brine.

After drying over Na<sub>2</sub>SO<sub>4</sub> and filtration, concentration of the solvent gave the crude product which was used directly in the next reaction without further purification.

## Example 265E

## benzyl 9-chloro-8-formyl-3-azaspiro[5.5]undec-8-ene-3-carboxylate

Phosphorus oxychloride (2.33 mL) was added dropwise to a cooled (0° C.) solution of EXAMPLE 265D (7.5 g) in N,N-dimethylformamide (10 mL) and dichloromethane (30 mL). The mixture was then stirred overnight before it was diluted with ethyl acetate (300 mL) and washed with aqueous sodium acetate, water (3×), and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the crude product was used directly in the next reaction without further purification.

## Example 265F

## benzyl 9-(4-chlorophenyl)-8-formyl-3-azaspiro[5.5]undec-8-ene-3-carboxylate

To a mixture of 4-chlorophenylboronic acid (5.94 g), EXAMPLE 265E (11.01 g), palladium(II) acetate (142 mg), K<sub>2</sub>CO<sub>3</sub> (13.2 g) and tetrabutylammonium bromide (10.2 g) was added water (120 mL). The mixture was stirred at 50° C. overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with water (3×) and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the residue was loaded on a column and eluted with 5 to 20% ethyl acetate in hexane to provide the title compound.

## Example 265G

## benzyl 8-((4-(3-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(methoxycarbonyl)phenyl)piperazin-1-yl)methyl)-9-(4-chlorophenyl)-3-azaspiro[5.5]undec-8-ene-3-carboxylate

To a solution of EXAMPLE 15F (1.37 g) and EXAMPLE 265F (1.65 g) in dichloromethane (20 mL) was added sodium

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triaceoxyborohydride (1.24 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous NaOH, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

## Example 265H

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-(9-(4-chlorophenyl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

EXAMPLE 265G (2 g) and tetrahydrofuran (10 mL) were added to 20% Pd(OH)<sub>2</sub>-C, wet (0.400 g) in a 50 mL pressure bottle and stirred for 16 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and evaporation of the solvent gave the title compound.

## Example 265I

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-(9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 265H (320 mg) in dichloromethane (5 mL) was added 1,3-difluoroacetone (139 mg) and sodium triaceoxyborohydride (157 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous NaOH, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

## Example 265J

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-(9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

To a solution of EXAMPLE 265I (320 mg) in tetrahydrofuran (4 mL) and methanol (2 mL) was added LiOH·H<sub>2</sub>O (120 mg) and the solution was stirred overnight. The reaction was cooled, carefully neutralized with 1N aqueous HCl and extracted with dichloromethane (3×50 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered and concentrated under vacuum to provide the title compound.

## Example 265K

## 4-(4-([9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 265J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (s, 1H), 8.49 (d, 2H), 7.72 (m, 1H), 7.49 (m, 2H), 7.32 (d, 2H), 7.07 (m, 3H), 6.65 (dd, 1H), 6.35 (d, 1H), 6.20 (m, 1H), 4.66 (m, 2H), 4.50 (m, 2H), 3.84 (m, 2H), 3.04 (m, 5H), 2.70 (m, 6H), 2.23 (m, 6H), 2.00 (m, 4H), 1.35 (m, 12H).



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## Example 266

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 266A

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 265H (320 mg) in dichloromethane (5 mL) was added acetone (143 mg) and sodium triacetoxyborohydride (157 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous

NaOH, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

## Example 266B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 266A for EXAMPLE 265I in EXAMPLE 265J.

## Example 266C

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.54 (s, 1H), 8.38 (m, 2H), 7.93 (d, 1H), 7.60 (m, 3H), 7.39 (m, 4H), 7.09 (d, 2H), 6.85 (d, 1H), 6.63 (dd, 1H), 6.27 (dd, 2H), 3.84 (m, 3H), 3.08 (m, 8H), 2.71 (s, 3H), 2.15 (m, 8H), 1.71 (m, 9H), 1.24 (m, 11H).

## Example 267

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 265J for EXAMPLE 1E and EXAMPLE 40B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.38 (s, 1H), 8.06 (m, 1H), 7.57 (d, 1H), 7.38 (m, 5H), 7.07 (m, 3H), 6.64 (dd, 1H), 6.33

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(d, 1H), 6.23 (m, 1H), 4.68 (d, 2H), 4.52 (d, 2H), 4.21 (d, 2H), 3.86 (dd, 2H), 3.08 (m, 8H), 2.71 (m, 6H), 2.10 (m, 12H), 1.42 (m, 7H).

## Example 268

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E and EXAMPLE 40B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.49 (s, 1H), 8.28 (d, 1H), 7.94 (dd, 2H), 7.60 (d, 1H), 7.35 (m, 4H), 7.08 (m, 2H), 6.61 (dd, 1H), 6.28 (dd, 2H), 4.18 (d, 2H), 3.85 (m, 2H), 3.05 (m, 7H), 2.71 (s, 3H), 2.25 (m, 6H), 2.02 (m, 2H), 1.63 (m, 8H), 1.30 (m, 9H).

## Example 269

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 269A

5-chloro-6-((4-fluoro-1-methylpiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.131 g) in N,N-dimethylformamide (3.0 mL) was treated with iodomethane (0.043 g) and sodium carbonate (0.079 g) and stirred at ambient temperature for 3 days. The N,N-dimethylformamide was removed on high vacuum and the concentrate was chromatographed on amine functionalized silica gel with 0 to 2% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 269B

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 269A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.11 (d, 1H), 8.71 (d, 1H), 8.44 (d, 1H), 8.16 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.49 (dd, 1H), 4.49 (d, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.68 (m, 2H), 2.38 (m, 2H), 2.26 (m, 5H), 2.14 (t, 4H), 1.97 (m, 6H), 1.39 (t, 2H), 0.94 (s, 6H).

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Example 270

N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-  
(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-  
1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]  
pyridin-5-yloxy)benzamide

Example 270A

5-chloro-6-((1-(2-(dimethylamino)acetyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.131 g), 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.139 g), and sodium carbonate (0.048 g) were combined in a 5-mL vial with N,N-dimethylformamide (3.0 mL) and stirred overnight at ambient temperature. Additional sodium carbonate (0.048 g) was added followed by 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.139 g) and stirring was continued over a second night. The reaction mixture was concentrated under high vacuum, slurried in CH<sub>2</sub>Cl<sub>2</sub>, filtered, concentrated and chromatographed on amine functionalized silica gel with 0 to 4% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

Example 270B

N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-  
(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-  
1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]  
pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 270A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 9.12 (d, 1H), 8.73 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.66 (d, 1H), 4.52 (dd, 2H), 4.07 (d, 1H), 3.46 (m, 1H), 3.40 (m, 1H), 3.30 (m, 1H), 3.11 (m, 1H), 3.06 (m, 4H), 2.77 (s, 2H), 2.35 (s, 6H), 2.26 (t, 2H), 2.14 (m, 4H), 2.05 (m, 2H), 1.97 (s, 2H), 1.81 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

Example 271

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 271A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidine-1-carboxylate

A solution of EXAMPLE 263E (2.0 g) and diethylamino-sulfur trifluoride (1.39 mL) in dichloromethane (40 mL) was stirred for 24 hours. The reaction was quenched with water (30 mL), extracted twice with ether, and the combined extracts were washed with water, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was

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chromatographed on silica gel using 5% ethyl acetate in hexanes to provide the title compound.

Example 271B

4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidine

The title compound was prepared by substituting EXAMPLE 271A for EXAMPLE 1A in EXAMPLE 1B.

Example 271C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 271B for EXAMPLE 263G in EXAMPLE 263H.

Example 271D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 271C for EXAMPLE 3I in EXAMPLE 3J.

Example 271E

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 271D for EXAMPLE 1E EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.46 (br s, 1H), 8.62 (t, 1H), 8.56 (d, 1H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.52 (m, 3H), 7.44 (d, 2H), 7.28 (m, 5H), 7.14 (m, 1H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.19 (d, 1H), 3.84 (dd, 2H), 3.31 (m, 9H), 2.95 (d, 2H), 2.81 (m, 2H), 1.91 (m, 1H), 1.62 (m, 2H), 1.45 (m, 2H), 1.29 (m, 2H).

Example 272

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 271D for EXAMPLE 1E and EXAMPLE 96A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.64 (br s, 1H), 8.58 (m, 1H), 8.25 (m, 1H), 8.03 (d, 1H), 7.70 (dd, 1H), 7.50 (m, 4H), 7.43 (m, 3H), 7.28 (m, 4H), 7.15 (m, 1H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.19 (d, 1H), 4.54 (d, 2H), 4.04 (m, 1H), 3.75

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(m, 2H), 3.58 (m, 2H), 2.95 (d, 2H), 2.80 (m, 2H), 1.88 (m, 2H), 1.82 (m, 2H), 1.48 (m, 2H), 1.28 (m, 2H), 0.85 (m, 2H).

## Example 273

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E and EXAMPLE 42A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.57 (s, 1H), 7.97 (d, 1H), 7.77 (s, 1H), 7.55 (m, 2H), 7.45 (m, 1H), 7.36 (m, 3H), 7.08 (d, 2H), 6.62 (dd, 2H), 6.35 (dd, 1H), 6.21 (d, 1H), 3.82 (m, 3H), 3.06 (m, 9H), 2.72 (m, 3H), 2.25 (m, 8H), 2.09 (m, 2H), 1.56 (m, 9H), 1.20 (m, 10H).

## Example 274

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 274A

(R)-5-chloro-6-(1-(3-fluoro-2-(fluoromethyl)propyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 261B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 274B

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 274A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.52 (s, 1H), 8.32 (d, 1H), 8.01 (d, 1H), 7.93 (d, 1H), 7.59 (d, 1H), 7.42 (m, 1H), 7.33 (m, 3H), 7.05 (d, 2H), 6.63 (dd, 1H), 6.31 (dd, 1H), 6.25 (d, 1H), 5.38 (m, 1H), 4.65 (t, 2H), 4.53 (t, 2H), 3.02 (s, 4H), 2.94 (m, 5H), 2.75 (s, 2H), 2.66 (m, 1H), 2.23 (m, 7H), 1.96 (s, 2H), 1.82 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 275

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 275A

3-(2-(benzyloxy)ethoxy)tetrahydrofuran

Tetrahydrofuran-3-ol (0.881 g) in tetrahydrofuran (15 mL) was treated with 60% sodium hydride (0.8 g). After 10 min-

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utes, ((2-bromoethoxy)methyl)benzene (3.23 g) was added. The solution was stirred for 16 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was separated, and was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 1:1 ethyl acetate:hexane to provide the title compound.

## Example 275B

2-(tetrahydrofuran-3-yloxy)ethanol

EXAMPLE 275A (0.85 g) and 5% palladium on carbon (0.1 g) in ethanol (10 mL) was treated with a balloon of hydrogen. The reaction was stirred overnight. The solid was filtered off, and the filtrate was concentrated to give the title compound.

## Example 275C

3-nitro-4-(2-(tetrahydrofuran-3-yloxy)ethoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 275B for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 275D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 275C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.32 (s, 1H), 8.00-8.02 (m, 2H), 7.49-7.52 (m, 2H), 7.39-7.41 (m, 1H), 7.38 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.33-4.35 (m, 2H), 4.18-4.21 (m, 1H), 3.62-3.67 (m, 4H), 3.09 (s, 4H), 2.83 (s, 2H), 2.26 (s, 2H), 2.15 (s, 2H), 1.96 (s, 2H), 1.85-1.94 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

## Example 276

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 276A

trans-4-(aminomethyl)cyclohexanecarbonitrile

To a solution of tert-butyl (trans-4-(cyanomethyl)cyclohexyl)methylcarbamate (500 mg) in dichloromethane (10 mL) was slowly added trifluoroacetic acid (2 mL) at 0° C. The reaction mixture was warmed to room temperature, stirred for 1 hour and concentrated to provide the title compound.

## Example 276B

4-((trans-4-cyanocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (347 mg) and EXAMPLE 276A (300 mg) in tetrahydrofuran (20

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mL) was treated with triethylamine (1.4 mL) overnight and concentrated. The residue was triturated with ethyl acetate to provide the title compound.

## Example 276C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((trans-4-cyanocyclohexyl)methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 276B in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.36 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47-7.54 (m, 3H), 7.34 (d, 2H), 7.01-7.09 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.25 (t, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.57-2.68 (m, 1H), 2.17 (d, 6H), 1.92-2.06 (m, 4H), 1.78 (d, 2H), 1.66 (s, 1H), 1.35-1.53 (m, 4H), 0.96-1.10 (m, 2H), 0.92 (s, 6H).

## Example 277

N-([5-chloro-6-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 277A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

## Example 277B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 277A (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

## Example 277C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl) methanol

To a mixture of LiBH<sub>4</sub> (13 g), EXAMPLE 277B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted

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with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

## Example 277D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 277C (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 277E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 277D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 277F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 277G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 277F (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M NaOH (69 mL) was added, followed by 30% H<sub>2</sub>O<sub>2</sub> (8.43 mL), and the solution was stirred for 1 hour. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH<sub>2</sub>PO<sub>4</sub>. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.



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## Example 277H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 277G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and  $K_3PO_4$  (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 277I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 277H (1.55 g), EXAMPLE 277E (2.42 g), and  $HK_2PO_4$  (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed three times with 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 277J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 277I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to  $NaH_2PO_4$  solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 277K

5,6-dichloropyridine-3-sulfonamide

To a solution of 5,6-dichloropyridine-3-sulfonyl chloride (32.16 g) in isopropyl alcohol (300 mL) at 0° C. was added a 30% aqueous solution of  $NH_4OH$  (50.8 mL). After stirring overnight, the solvent was reduced to 1/3 of the original volume. It was then partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over  $MgSO_4$ , filtered, and concentrated. The residue was chromatographed on silica gel. The material was then slurried in 1:9 ethyl acetate/hexanes, filtered and dried under vacuum to give the title compound.

## Example 277L

tert-butyl

4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (5 mL) was treated with 1.0 N  $LiAlH_4$  in tetrahydrofuran (2.54 mL) at 0° C. The reaction mixture was stirred at room temperature for 2 hours. Water (0.6 mL) was added to the reaction mixture drop-wise, followed by 2 N aqueous NaOH (0.2 mL). The reaction was stirred for another 1 hour. The solid was removed by filtration via a pack of diatomaceous earth and washed with ethyl

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acetate. The filtrate was washed with brine, dried over  $MgSO_4$ , filtered, and concentrated to give the product.

## Example 277M

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

To a solution of EXAMPLE 277L (1 g) in tetrahydrofuran (15 mL) was added NaH (60% dispersion in mineral oil, 685 mg), and the solution was stirred for 10 minutes. EXAMPLE 277K (1 g) was added and the reaction stirred for 24 hours. The mixture was poured into water, neutralized with 10% HCl, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over  $MgSO_4$ , filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 30% ethyl acetate in hexanes.

## Example 277N

5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

EXAMPLE 277M (13 mL) was treated with trifluoroacetic acid (2.363 mL), stirred at ambient temperature for 2 hours, concentrated and dried to give the title compound.

## Example 277O

5-chloro-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 277N (0.088 g) and oxetan-3-one (0.014 g) were combined in dichloromethane (2.0 mL) and dimethylformamide (1.0 mL) and stirred at ambient temperature for 45 minutes. Sodium triacetoxyborohydride (0.064 g) was added in portions. Stirring was continued overnight at ambient temperature. Additional oxetan-3-one (0.014 g) was added and stirring was continued for 30 minutes at ambient temperature before more sodium triacetoxyborohydride (0.064 g) was added. The reaction mixture was stirred for 72 hours at ambient temperature, concentrated, chromatographed on silica gel with 0 to 5% methanol in dichloromethane as the eluent, and dried in a vacuum oven at 80° C. to give the title compound.

## Example 277P

N-[(5-chloro-6-[[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 277J (0.063 g), EXAMPLE 277O (0.042 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.032 g), and 4-dimethylaminopyridine (0.027 g) were combined in a 4-mL vial with dichloromethane (1.0 mL) and stirred overnight at ambient temperature. The reaction mixture was chromatographed directly without aqueous workup on silica gel with 0-4% methanol in dichloromethane as the eluent. Fractions containing the desired product were concentrated, slurried in acetonitrile, concentrated and dried overnight in a vacuum oven at 80° C. to give the title compound.  $^1H$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.05 (s, 1H), 9.13 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.67 (m, 1H), 7.66 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.51

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(m, 2H), 4.63 (m, 4H), 4.53 (d, 2H), 3.39 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.51 (m, 2H), 2.25 (m, 2H), 2.18 (m, 2H), 2.13 (m, 4H), 2.06 (t, 2H), 1.97 (s, 2H), 1.89 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 278

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 278A

5-bromo-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-(tetrahydro-2H-pyran-4-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 36B.

## Example 278B

5-cyano-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 278A for EXAMPLE 36B in EXAMPLE 36C.

## Example 278C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 278B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 7.96 (d, 1H), 7.56 (d, 1H), 7.45-7.47 (m, 1H), 7.40 (s, 1H), 7.36 (d, 2H), 7.06 (d, 2H), 6.67 (dd, 1H), 6.34 (dd, 1H), 6.25 (d, 1H), 4.47 (d, 2H), 3.80-3.84 (m, 2H), 3.24-3.28 (m, 2H), 3.12 (s, 2H), 2.16 (s, 2H), 1.97 (s, 2H), 1.61-1.71 (m, 4H), 1.40 (t, 2H), 1.21-1.25 (m, 2H), 0.93 (s, 6H).

## Example 279

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 279A

4-(furan-3-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting furan-3-ylmethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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## Example 279B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared by substituting EXAMPLE 279A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.34 (s, 1H), 8.03-8.06 (m, 2H), 7.83 (s, 1H), 7.69 (t, 1H), 7.51-7.53 (m, 4H), 7.34-7.36 (m, 2H), 7.04-7.06 (m, 2H), 6.68 (dd, 1H), 6.57 (s, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 5.23 (s, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.15-2.32 (m, 6H), 1.39 (t, 2H), 0.92 (s, 6H).

## Example 280

N-[(5-chloro-6-({(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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## Example 280A

(R)-tert-butyl 3-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)pyrrolidine-1-carboxylate

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The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and (R)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 280B

(R)-5-chloro-6-(pyrrolidin-3-ylmethoxy)pyridine-3-sulfonamide

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The title compound was prepared by substituting EXAMPLE 280A for tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

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## Example 280C

(R)-5-chloro-6-((1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

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The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 280B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 280D

N-[(5-chloro-6-({(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

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The title compound was prepared by substituting EXAMPLE 280C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.57 (s, 1H), 8.38 (d, 1H), 8.07 (d, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.44 (m, 1H), 7.35 (m, 3H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.33 (dd, 1H),

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6.23 (d, 1H), 4.65 (d, 2H), 4.53 (dd, 2H), 2.92 (m, 8H), 2.75 (m, 4H), 2.58 (m, 2H), 2.20 (m, 6H), 1.96 (m, 4H), 1.53 (m, 1H), 1.39 (t, 2H), 0.89 (s, 6H).

## Example 281

N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 281A

(R)-5-chloro-6-((1-(2,2-difluoro ethyl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 280B for EXAMPLE 261B in EXAMPLE 261C.

## Example 281B

N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 281A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.98 (d, 1H), 7.56 (d, 1H), 7.46 (m, 1H), 7.41 (d, 1H), 7.34 (d, 2H), 7.04 (d, 2H), 6.65 (dd, 1H), 6.35 (dd, 1H), 6.23 (m, 1H), 6.03 (m, 1H), 3.06 (s, 4H), 2.84 (m, 6H), 2.63 (m, 4H), 2.20 (m, 6H), 1.94 (m, 3H), 1.53 (m, 1H), 1.39 (t, 2H), 0.91 (s, 6H).

## Example 282

N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 282A

5-chloro-6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.088 g) and 1,3-difluoropropan-2-one (0.028 g) were combined in dichloromethane (2 mL) and N,N-dimethylformamide (0.500 mL) and stirred at ambient temperature for 45 minutes. Sodium triacetoxymethylborohydride (0.064 g) was added in portions and then the reaction mixture was stirred overnight at ambient temperature. Additional 1,3-difluoropropan-2-one (0.028 g) was added, followed 30 minutes later by the addition of more sodium triacetoxymethylborohydride (0.064 g). The reaction mixture was stirred at ambient temperature for 72 hours. Additional 1,3-difluoropropan-2-one (0.028 g) was again added, followed 30 minutes later by the addition of more sodium triacetoxymethylborohydride (0.064 g). The reaction mixture was stirred overnight at ambient temperature. Additional 1,3-difluoropropan-2-one (0.028 g) was again added, followed 30 minutes later by the addition of more sodium triacetoxymethylborohydride (0.064 g). The reaction mixture was stirred overnight at ambient temperature. The

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reaction mixture was concentrated under high vacuum to remove N,N-dimethylformamide and then chromatographed on silica gel with 0 to 4% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 282B

N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 282A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.12 (t, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 4.77 (dd, 1H), 4.65 (dd, 1H), 4.52 (dd, 2H), 3.06 (m, 4H), 2.93 (t, 1H), 2.80 (m, 5H), 2.52 (m, 1H), 2.26 (t, 2H), 2.13 (m, 4H), 2.04 (m, 2H), 1.97 (s, 2H), 1.85 (m, 2H), 1.39 (t, 2H), 1.28 (m, 2H), 0.93 (s, 6H).

## Example 283

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 283A

3-chloro-4-((4-fluoro-1-methylpiperidin-4-yl)methoxy)benzenesulfonamide

To a solution of (4-fluoro-1-methylpiperidin-4-yl)methanol (0.265 g) in tetrahydrofuran (2 mL) was added sodium hydride (0.288 g). After 15 minutes, 3-chloro-4-fluorobenzenesulfonamide (0.377 g) was added as a solution in tetrahydrofuran (1 mL). The reaction was stirred for 2 hours, quenched with water (5 mL), adjusted to pH~7 with 1N aqueous HCl, and extracted with dichloromethane (2x25 mL). The organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.1% to 10% methanol containing 2N NH<sub>3</sub>/dichloromethane over 30 minutes gave the title compound.

## Example 283B

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 283A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 10.68-9.84 (m, 1H), 7.99 (d, 1H), 7.79 (d, 1H), 7.63 (t, 1H), 7.54 (d, 1H), 7.50-7.38 (m, 2H), 7.34 (d, 2H), 7.04 (d, 3H), 6.64 (dd, 1H), 6.36 (dd, 1H),

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6.22 (s, 1H), 4.23 (d, 2H), 3.03 (s, 6H), 2.71 (m, 4H), 2.07 (m, 12H), 1.38 (s, 3H), 1.24 (s, 2H), 0.92 (s, 6H).

## Example 284

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 284A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

To a solution of (tetrahydro-2H-pyran-4-yl)methanol (0.258 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.355 g) and the reaction stirred at room temperature for 15 minutes. EXAMPLE 52A (0.400 g) was added and the reaction stirred for an additional 1 hour. The reaction was poured into ethyl acetate (50 mL) and 1N aqueous HCl (35 mL). The organic layer was washed with brine (35 mL) dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 10% to 100% ethyl acetate/hexanes over 30 minutes gave the title compound.

## Example 284B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 284A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.60-11.16 (m, 1H), 8.15 (s, 1H), 8.08-8.01 (m, 2H), 7.58-7.46 (m, 3H), 7.35 (d, J=8.4, 2H), 7.29 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.05 (d, 2H), 3.89 (d, 2H), 3.37 (d, 4H), 3.09 (s, 4H), 2.81 (s, 2H), 2.21 (d, 7H), 1.96 (s, 2H), 1.67 (d, 2H), 1.39 (s, 2H), 0.92 (s, 6H).

## Example 285

N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 285A

5-chloro-6-((1-(2,2-difluoro ethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.263 g), 1,1-difluoro-2-iodoethane (0.23 g), and sodium carbonate (0.254 g) were combined in a 20-mL vial with N,N-dimethylformamide (6 mL) and stirred at 70° C. overnight. The reaction mixture was concentrated

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under high vacuum and then chromatographed on silica gel with 0 to 5% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 285B

N-[(5-chloro-6-{[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 285A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.12 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.43 (m, 2H), 7.06 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 6.18 (tt, 2H), 4.51 (d, 2H), 3.07 (m, 4H), 2.80 (m, 6H), 2.60 (td, 2H), 2.25 (t, 2H), 2.13 (m, 4H), 2.03 (t, 2H), 1.97 (s, 2H), 1.93 (m, 1H), 1.85 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 286

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 286A

3-chloro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (4-fluoro-1-methylpiperidin-4-yl) methanol in EXAMPLE 283A.

## Example 286B

N-({3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 286A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.56-11.16 (m, 1H), 8.06 (d, 1H), 7.90 (d, 1H), 7.81 (d, 1H), 7.64-7.45 (m, 3H), 7.34 (d, 2H), 7.26 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.42 (dd, 1H), 6.18 (s, 1H), 4.28 (d, 2H), 3.78 (d, 2H), 3.61 (dd, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.17 (d, 6H), 1.87 (dd, 6H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 287

N-({5-chloro-6-[(4,4-difluoro cyclo hexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 287A

(4,4-difluorocyclohexyl)methanol

Ethyl 4,4-difluorocyclohexanecarboxylate (1.0 g, 5.20 mmol) in diethyl ether (2 mL) was added dropwise to lithium



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aluminium hydride (0.24 g) in diethyl ether (15 mL), and heated under reflux for 4 hours. The reaction was then cooled to 0° C., and water was added (0.24 mL), followed by 5N aqueous NaOH (0.24 mL) and water (0.72 mL). Then Na<sub>2</sub>SO<sub>4</sub> and more diethyl ether (40 mL) were added, and the mixture was stirred for 30 minutes, then filtered through celite. After concentration, the residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> and Na<sub>2</sub>SO<sub>4</sub> was added, and the mixture was filtered and concentrated to provide the title compound.

## Example 287B

## 5-chloro-6-((4,4-difluorocyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 287A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 287C

## N-({5-chloro-6-[(4,4-difluoro cyclo hexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 287B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.46 (d, 1H), 8.14 (d, 1H), 8.00 (d, 1H), 7.56 (d, 1H), 7.47 (m, 2H), 7.35 (d, 2H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.25 (d, 2H), 3.07 (br m, 4H), 2.82 (br s, 2H), 2.30 (br m, 4H), 2.16 (br m, 2H), 2.00, 1.95, 1.85 (all m, total 9H), 1.40 (t, 2H), 1.37 (m, 2H), 0.92 (s, 6H).

## Example 288

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{6-{{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl}sulfonyl}}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 288A

## 5-Nitro-3-(trifluoromethyl)pyridin-2-ol

3-(Trifluoromethyl)pyridin-2-ol (2.3 g) was added to concentrated sulfuric acid (15 mL) at 0° C. The mixture was stirred at 0° C. for 5 minutes. To this solution was added fuming nitric acid (6 mL) dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 2 hours, and then heated at 50° C. for 3 hours. After cooling, the reaction mixture was poured onto ice (200 g), and the mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide the title compound.

## Example 288B

## 2-Chloro-5-nitro-3-(trifluoromethyl)pyridine

A mixture of EXAMPLE 288A (1.69 g), phosphorus pentachloride (2.03 g), and phosphoryl trichloride (0.97 mL) was heated at 90° C. for 3 hours. After cooling, the reaction

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mixture was poured into ice, and extracted with ethyl acetate three times. The extract was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in hexanes to provide the title compound.

## Example 288C

## 6-Chloro-5-(trifluoromethyl)pyridin-3-amine

A mixture of iron (1.5 g) and ammonium chloride (2.38 g) in water (40 mL) was stirred at room temperature for 5 minutes. To this suspension was added EXAMPLE 288B in methanol (40 mL). The reaction mixture was stirred at room temperature for 1 hour. More iron (1.8 g) was added to the reaction mixture, and it was stirred for another 3 hours. The solid from the reaction mixture was filtered off, and the filtrate was partitioned between water and ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 20% ethyl acetate in hexanes to provide the title compound.

## Example 288D

## 6-chloro-5-(trifluoromethyl)pyridine-3-sulfonyl chloride

Under ice-cooling, thionyl chloride (4 mL) was added dropwise over 20 minutes to water (27 mL). The mixture was stirred overnight for 12 hours to give a SO<sub>2</sub> containing solution. Separately, EXAMPLE 288C (1.14 g) in dioxane (5 mL) was added to concentrated HCl (20 mL) at 0° C. The solution was stirred for 5 minutes. To this suspension/solution was added sodium nitrite (0.44 g) in water (6 mL) dropwise at 0° C. The solution was stirred at 0° C. for 3 hours. During this time, any solid formed was crushed with a glass rod to make sure that EXAMPLE 288C was completely reacted. To the SO<sub>2</sub> containing solution was added copper(I) chloride (0.115 g). Then, to this solution was added the diazotized EXAMPLE 288C at 0° C. The solution was stirred for 30 minutes. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to provide the title compound.

## Example 288E

## 6-chloro-5-(trifluoromethyl)pyridine-3-sulfonamide

EXAMPLE 288D (2.03 g) in dioxane (20 mL) solution was cooled to 0° C. Ammonium hydroxide solution was added dropwise. The reaction mixture was stirred at 0° C. for 2 hours followed by room temperature over night. The solvent was partially removed, and the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 0-3% methanol in dichloromethane to afford the title compound.

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## Example 288F

tert-butyl 4-fluoro-4-((5-sulfamoyl-3-(trifluoromethyl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 322A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 288G

6-((4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288F for tert-butyl (4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

## Example 288H

6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 288G for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 288I

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-([1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 288H for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.57 (s, 1H), 8.27 (d, 1H), 7.91 (d, 1H), 7.58 (d, 1H), 7.40 (m, 1H), 7.35 (d, 2H), 7.28 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.29 (dd, 1H), 6.24 (d, 1H), 4.67 (d, 2H), 4.55 (d, 2H), 4.50 (s, 1H), 4.44 (s, 1H), 3.06 (m, 5H), 2.73 (m, 6H), 2.19 (d, 6H), 1.90 (m, 7H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 289

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-chloro-6-[2-(tetrahydro furan-2-yl)ethoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 289A

5-chloro-6-(2-(tetrahydrofuran-2-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-(tetrahydro-2H-pyran-4-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

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## Example 289B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-chloro-6-[2-(tetrahydro furan-2-yl)ethoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 289A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.52 (d, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.50-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.39-4.51 (m, 4H), 3.87-3.94 (m, 1H), 3.73-3.78 (m, 1H), 3.57-3.62 (m, 1H), 3.11 (s, 4H), 2.89 (s, 2H), 2.33 (s, 4H), 2.15 (s, 2H), 1.77-2.01 (m, 7H), 1.45-1.54 (m, 1H), 1.40 (t, 2H), 0.93 (s, 6H).

## Example 290

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)-3-methylpiperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 290A

2-chloro-4,4-dimethylcyclohex-1-enecarbaldehyde

Into a 250 ml round-bottomed flask was added N,N-dimethylformamide (3.5 mL) in dichloromethane (30 mL). The mixture was cooled to -10° C., and phosphoryl trichloride (4 mL) was added dropwise. The solution was warmed up to room temperature and 3,3-dimethylcyclohexanone (5.5 mL) was added slowly. The mixture was heated to reflux overnight. The reaction mixture was quenched by 0° C. solution of sodium acetate (25 g in 50 mL water). The aqueous layer was extracted with ether (3×200 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and dried under vacuum.

## Example 290B

2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarbaldehyde

Into a 1 L round-bottomed flask was added EXAMPLE 290A (6.8 g), 4-chlorophenylboronic acid (6.5 g) and palladium(II) acetate (0.2 g) in water (100 mL) to give a suspension. Potassium carbonate (15 g) and tetrabutylammonium bromide (10 g) were added. After degassing after subjecting to vacuum and nitrogen, the mixture was stirred at 45° C. for 4 hours. After filtering through silica gel, diethyl ether (4×200 mL) was used to extract the product. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated and purified by flash chromatography on silica with 0-10% ethyl acetate in hexanes to provide the title compound.

## Example 290C

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazine-1-carboxylate

To a solution of tert-butyl 3-methylpiperazine-1-carboxylate (0.256 g) and EXAMPLE 290B (0.350 g) in dichloro-

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romethane (2 mL) was added sodium triacetoxyborohydride (0.406 g) and the reaction was stirred at room temperature overnight. The reaction was quenched with NaHCO<sub>3</sub> solution (50 mL) and extracted with dichloromethane (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.5% to 2.5% methanol/dichloromethane gave the title compound.

## Example 290D

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-2-methylpiperazine

A solution of EXAMPLE 290C (0.298 g) and HCl (4.0M in dioxane, 2 mL) were stirred for 1 hour. The reaction was concentrated and partitioned between dichloromethane (100 mL) and NaHCO<sub>3</sub> (100 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated to provide the title compound.

## Example 290E

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 290D for EXAMPLE 3E in EXAMPLE 3I.

## Example 290F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 290E for EXAMPLE 15G in EXAMPLE 15H.

## Example 290G

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)-3-methylpiperazin-1-yl)-N-([3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 290F for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.54-11.30 (m, 1H), 8.62-8.53 (m, 2H), 8.03 (d, 1H), 7.78 (d, 1H), 7.48 (d, 3H), 7.34 (d, 2H), 7.06 (t, 3H), 6.68 (d, 1H), 6.38 (dd, 1H), 6.21 (s, 1H), 3.84 (d, 2H), 3.23 (s, 4H), 2.75 (s, 4H), 1.64 (s, 8H), 1.62 (d, 2H), 1.42-1.17 (m, 6H), 0.92 (s, 6H), 0.87 (s, 3H).

## Example 291

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([3-(cyclopropylamino)propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 291A

tert-butyl 2-cyanoethyl(cyclopropyl)carbamate

To a solution of 3-(cyclopropylamino)propanenitrile (5.0 g) in tetrahydrofuran (30 mL) was added di-tert-butyl dicar-

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bonate (9.91 g) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with 5% aqueous HCl, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered, and the solvent was evaporated under vacuum to provide the title compound.

## Example 291B

tert-butyl 3-aminopropyl(cyclopropyl)carbamate

EXAMPLE 291A (9.75 g) and 7M NH<sub>3</sub>-methanol (25 mL) were added to a Ra-Ni 2800, water slurry (19.50 g, 332 mmol) in a 250 mL pressure bottle and stirred for 2 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and evaporation of the solvent gave the title compound.

## Example 291C

tert-butyl cyclopropyl(3-(2-nitro-4-sulfamoylphenylamino)propyl)carbamate

To a solution of 4-chloro-3-nitrobenzenesulfonamide (2.5 g), and EXAMPLE 291B (2.26 g) in dioxane (20 mL) was added N,N-diisopropylethylamine (5 mL). The mixture was stirred at reflux overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered, and the solvent was evaporated under vacuum to provide the title compound.

## Example 291D

tert-butyl 3-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)propyl(cyclopropyl)carbamate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 291C for EXAMPLE 1F in EXAMPLE 1G.

## Example 291E

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([3-(cyclopropylamino)propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 291D (2.56 g) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 2 hours. The mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the crude product. The title compound was obtained by dissolving 200 mg of the crude material in dimethylsulfoxide/methanol (1:1, 10 mL) and loaded on Gilson, C18(100A) 250×121.2 mm (10 micron), eluting with 30% acetonitrile to 65% acetonitrile over 40 minutes. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.54 (s, 1H), 8.43 (m, 2H), 7.94 (d, 1H), 7.71 (dd, 1H), 7.57 (d, 1H), 7.43 (m, 1H), 7.34 (m, 3H), 7.05 (d, 2H), 6.90 (d, 1H), 6.63 (dd, 1H), 6.29 (d, 2H), 3.43 (m, 2H), 2.96 (m, 6H), 2.73 (m, 2H), 2.22 (m, 7H), 1.87 (m, 4H), 1.38 (m, 3H), 0.94 (m, 6H), 0.62 (m, 4H).

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## Example 292

N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 292A

5-chloro-6-(2-methoxyethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and 2-methoxyethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 292B

N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 292A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.48 (d, 1H), 8.17 (d, 1H), 8.01 (d, 1H), 7.56 (d, 1H), 7.49 (m, 2H), 7.35 (d, 2H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.52 (m, 2H), 3.70 (m, 2H), 3.28 (s, 3H), 3.13 (br m, 4H), 2.88 (br s, 2H), 2.34 (br m, 4H), 2.16 (br m, 2H), 1.97 (s, 2H), 1.40 (t, 2H), 0.92 (s, 6H).

## Example 293

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 293A

The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 293B

tert-butyl 5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

The title compound was prepared by substituting EXAMPLE 293A for EXAMPLE 248A in EXAMPLE 248B.

## Example 293C

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

The title compound was prepared by substituting EXAMPLE 293B for EXAMPLE 248B in EXAMPLE 248C.

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## Example 293D

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 293C for EXAMPLE 248C in EXAMPLE 248D.

## Example 293E

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 293D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.05 (d, 1H), 8.44 (dd, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.21 (d, 2H), 3.96 (dd, 2H), 3.31 (td, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (m, 3H), 1.58 (dd, 2H), 1.38 (m, 4H), 0.94 (s, 6H).

## Example 294

N-[(3-chloro-4-([1-(methoxyacetyl)piperidin-4-yl]methoxy)phenyl)sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 294A

tert-butyl 4-((2-chloro-4-sulfamoylphenoxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl-4-(hydroxymethyl)piperidine-1-carboxylate for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

## Example 294B

tert-butyl 4-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-chlorophenoxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 294A for EXAMPLE 1F in EXAMPLE 1G.

## Example 294C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(3-chloro-4-(piperidin-4-ylmethoxy)phenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

To EXAMPLE 294B (0.286 g) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the reaction stirred at room temperature. After 3 hours the reaction was concentrated to provide the title compound.



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## Example 294D

N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To EXAMPLE 294C (0.75 g) as a solution in dichloromethane (1 mL) was added N,N-diisopropylethylamine (0.055 mL) followed by 2-methoxyacetyl chloride (6 µl). After stirring for 10 minutes the reaction was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.5% to 3.5% methanol/dichloromethane over 30 minutes (flow=40 mL/minutes) to provide the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.55-11.24 (m, 1H), 8.06 (d, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.57 (s, 1H), 7.51 (s, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.21 (d, 1H), 7.04 (d, 2H), 6.67 (d, 1H), 6.42 (dd, 1H), 6.18 (s, 1H), 4.42-4.32 (m, 1H), 4.03 (dd, 4H), 3.86-3.74 (m, 1H), 3.28 (s, 3H), 3.07 (s, 5H), 2.77 (s, 3H), 2.30-1.92 (m, 9H), 1.77 (s, 2H), 1.31 (d, 4H), 0.92 (s, 6H).

## Example 295

N-[(3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride for 2-methoxyacetyl chloride in EXAMPLE 294D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 10.35-9.94 (m, 1H), 7.96 (d, 1H), 7.74 (d, 1H), 7.55 (d, 2H), 7.45 (s, 1H), 7.41-7.29 (m, 3H), 7.05 (d, 3H), 6.63 (d, 1H), 6.37-6.32 (m, 1H), 6.22 (d, 1H), 4.39 (d, 1H), 3.94 (s, 6H), 3.01 (s, 6H), 2.73 (m, 4H), 2.55 (m, 5H), 2.19 (s, 6H), 1.95 (m, 2H), 1.82 (m, 2H), 1.38 (s, 4H), 0.93 (s, 6H).

## Example 296

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 296A

tert-butyl 4-((4,4-dimethyl-2-oxocyclohexyl)methyl)piperidine-1-carboxylate

3,3-Dimethylcyclohexanone (5.60 mL) was added to sodium bis(trimethylsilyl)amide (45.3 mL, 1M in tetrahydrofuran), and the reaction was stirred for 1 hour. tert-Butyl 4-(bromomethyl)piperidine-1-carboxylate (11.1 g) in dimethylsulfoxide (30 mL) was added, and the reaction was stirred at 50° C. for 24 hours. The reaction was cooled, poured into water (300 mL), extracted three times with ether, and the combined extracts were washed three times with water, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-20% ethyl acetate in hexanes to provide the title compound.

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## Example 296B

tert-butyl 4-((2-(4-chlorophenyl)-2-hydroxy-4,4-dimethylcyclohexyl)methyl)piperidine-1-carboxylate

(4-Chlorophenyl)magnesium bromide (14.1 mL, 1M in ether) was added to EXAMPLE 296A (3.25 g) in tetrahydrofuran (40 mL) at -78° C., and the reaction was stirred for 20 minutes, and then allowed to warm to room temperature overnight. The reaction was quenched with pH 7 buffer (20 mL), extracted with 2x ether, and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 1-20% ethyl acetate in hexanes to provide the title compound.

## Example 296C

trans-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidine

The title compound was prepared by substituting EXAMPLE 296B for EXAMPLE 1A in EXAMPLE 1B.

## Example 296D

Trans-methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 296C for EXAMPLE 263G in EXAMPLE 263H.

## Example 296E

Trans-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 296D for EXAMPLE 3I in EXAMPLE 3J.

## Example 296F

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 296E for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.36 (br s, 1H), 8.60 (t, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.78 (dd, 1H), 7.52 (m, 3H), 7.27 (d, 2H), 7.16 (d, 2H), 7.09 (m, 1H), 6.63 (dd, 1H), 6.38 (dd, 1H), 6.11 (d, 1H), 3.83 (dd, 2H), 3.52 (m, 2H), 3.26 (m, 4H), 2.61 (m, 2H), 2.35 (m, 1H), 1.89

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(m, 2H), 1.76 (m, 1H), 1.62 (m, 2H), 1.38 (m, 4H), 1.25 (m, 6H), 1.12 (m, 2H), 0.95 (m, 2H), 0.94 (s, 3H), 0.88 (s, 3H).

## Example 297

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl]benzamide

## Example 297A

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 297B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl]benzamide

The title compound was prepared by substituting EXAMPLE 297A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.49 (s, 1H), 8.56 (d, 1H), 8.23 (d, 1H), 7.90 (d, 1H), 7.58 (d, 1H), 7.40 (m, 1H), 7.34 (m, 2H), 7.26 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.28 (dd, 1H), 6.24 (d, 1H), 4.24 (d, 2H), 3.86 (dd, 2H), 3.30 (m, 4H), 3.00 (s, 4H), 2.73 (s, 2H), 2.16 (m, 6H), 1.97 (m, 2H), 1.61 (dd, 2H), 1.33 (m, 4H), 0.93 (s, 6H).

## Example 298

N-({5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 298A

6-((trans-4-(tert-butyl)dimethylsilyloxy)cyclohexyl)methoxy)-5-chloropyridine-3-sulfonamide

The title compound was prepared by substituting (trans-4-(tert-butyl)dimethylsilyloxy)cyclohexyl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

## Example 298B

N-({5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 298A for EXAMPLE 11B in EXAMPLE 11D. After the reaction was over, the solvent was removed, and the residue was treated with 1:1 trifluoroacetic acid/dichlo-

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romethane for two hours. The solvents were removed, and the residue was purified by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 μA, C18(2), 250×21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% trifluoroacetic acid to provide the title compound. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 8.01 (d, 1H), 7.54 (d, 1H), 7.48-7.49 (m, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.21 (s, 1H), 4.53 (t, 1H), 4.18 (d, 2H), 3.08 (s, 4H), 2.84 (s, 2H), 2.29 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.79-1.83 (m, 5H), 1.39 (t, 2H), 1.08-1.13 (m, 5H), 0.93 (s, 6H).

## Example 299

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 299A

3-cyano-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 284A.

## Example 299B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 299A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.72 (s, 1H), 10.24-9.27 (m, 1H), 8.21 (d, 1H), 8.12 (dd, 1H), 8.05 (d, 1H), 7.63-7.46 (m, 3H), 7.45-7.31 (m, 3H), 7.07 (d, 2H), 6.70 (dd, 1H), 6.42 (s, 1H), 6.23 (s, 1H), 4.38 (d, 2H), 3.91-3.73 (m, 2H), 3.68-3.51 (m, 2H), 3.22-2.96 (m, 10H), 2.31-2.12 (m, 2H), 1.99 (s, 6H), 1.43 (t, 2H), 0.93 (s, 6H).

## Example 300

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 300A

6-((trans-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 121A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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## Example 300B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-((trans-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 300A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.56 (d, 1H), 8.23 (d, 1H), 7.90 (d, 1H), 7.58 (d, 1H), 7.40 (m, 1H), 7.35 (d, 2H), 7.27 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.28 (dd, 1H), 6.24 (d, 1H), 4.20 (d, 2H), 3.23 (s, 3H), 3.03 (m, 5H), 2.73 (s, 2H), 2.18 (m, 6H), 1.98 (m, 5H), 1.80 (m, 3H), 1.39 (t, 2H), 1.09 (m, 4H), 0.93 (s, 6H).

## Example 301

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-((cis-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 301A

6-((cis-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 121A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 301B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-((cis-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 301A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.49 (m, 1H), 8.54 (m, 1H), 8.23 (d, 1H), 7.91 (d, 1H), 7.59 (d, 1H), 7.40 (m, 1H), 7.34 (m, 2H), 7.27 (d, 1H), 7.04 (d, 2H), 6.61 (dd, 1H), 6.29 (dd, 1H), 6.24 (d, 1H), 4.20 (d, 2H), 3.37 (m, 2H), 3.19 (s, 3H), 3.00 (s, 4H), 2.73 (s, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.80 (m, 3H), 1.50 (dd, 2H), 1.37 (m, 6H), 0.93 (s, 6H).

## Example 302

N-([5-chloro-6-((4,4-difluoro-1-hydroxycyclohexyl)methoxy)pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 302A

4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidine

EXAMPLE 296B (1.0 g) was stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) at 35° C. for 48

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hours. The mixture was concentrated, taken up in dichloromethane (100 mL), and stirred, and saturated Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) was added slowly. The solution was separated and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

## Example 302B

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 302A for EXAMPLE 263G in EXAMPLE 263H.

## Example 302C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 302B for EXAMPLE 3I in EXAMPLE 3J.

## Example 302D

1,1-difluoro-4-methylenecyclohexane

Butyllithium (12.32 mL, 2.5 M solution in hexanes) was added to a solution of methyltriphenylphosphonium chloride (9.63 g) in tetrahydrofuran (50 mL) at 0° C., and the reaction was stirred for 5 minutes. 4,4-Difluorocyclohexanone (3.76 g) in dioxane (150 mL) was then added, and the reaction was stirred for 30 minutes. Water (3 mL) was added, and then hexane (150 mL) was slowly added, the reaction was filtered, and the solution carried on.

## Example 302E

4,4-difluoro-1-(hydroxymethyl)cyclohexanol

To the solution from EXAMPLE 302D was added water (75 mL), then N-methylmorpholine-N-oxide (6.4 mL, 50% solution in water) and OsO<sub>4</sub> (14.2 g, 2.5 wt % solution in tert-butanol) were added, and the reaction was stirred for 96 hours at 50° C. The solution was cooled to room temperature, treated with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (100 mL) for 30 minutes, and then acidified with concentrated aqueous HCl. The solution was then extracted three times with ethyl acetate, and the organic layers were combined, washed with 1M HCl, and brine, and concentrated. The crude mixture was chromatographed on silica gel using 10-100% ethyl acetate in hexanes, and then 5% methanol in ethyl acetate to give the product.

## Example 302F

5-chloro-6-((4,4-difluoro-1-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 302E for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

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## Example 302G

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 302F for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (br s, 2H), 8.51 (s, 1H), 8.18 (s, 1H), 8.02 (d, 1H), 7.53 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.69 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.88 (s, 1H), 4.27 (s, 2H), 3.10 (m, 4H), 2.88 (m, 1H), 2.33 (m, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.91 (m, 2H), 1.73 (m, 4H), 1.52 (m, 1H), 1.40 (m, 2H), 1.31 (m, 1H), 0.93 (s, 3H), 0.91 (m, 2H).

## Example 303

N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 303A

trans-4-morpholinocyclohexyl)methanol

To tert-butyl trans-4-(hydroxymethyl)cyclohexylcarbamate (0.500 g) was added hydrogen chloride (4.0M in dioxane, 2.2 mL) and the reaction was stirred for 1 hour and concentrated. The resulting solid was dissolved in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (1.523 mL) followed by 1-bromo-2-(2-bromoethoxy)ethane (0.556 g) and heated to 60° C. After stirring overnight the reaction was concentrated, loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 1% to 10% methanol/dichloromethane over 30 minutes (flow=40 mL/min) to provide the title compound.

## Example 303B

3-chloro-4-(((1r,4r)-4-morpholinocyclohexyl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 303A for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

## Example 303C

N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 303B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 10.96-10.59 (m, 1H), 8.02 (d, 1H), 7.82 (d, 1H), 7.69 (s, 1H), 7.50 (dd, 3H), 7.38-7.30 (m, 2H), 7.15-6.99 (m, 3H), 6.65 (dd, 1H), 6.39 (dd, 1H), 6.20

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(d, 1H), 3.91 (d, 2H), 3.64 (s, 4H), 3.04 (s, 4H), 2.73 (s, 7H), 2.18 (s, 6H), 1.93 (m, 6H), 1.80-1.65 (m, 1H), 1.32 (m, 6H), 0.92 (s, 6H).

## Example 304

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-({3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 291E (95 mg) in dichloromethane (2 mL) and acetic acid (0.5 mL) was added thiazole-5-carbaldehyde (13 mg) followed by sodium triacetoxyborohydride (35 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave crude product which was dissolved in dimethylsulfoxide/methanol (6 mL, 1:1) and loaded on Gilson, C18(100A) 250×121.2 mm (10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.95 (s, 1H), 8.57 (m, 2H), 8.03 (d, 1H), 7.78 (m, 2H), 7.49 (m, 3H), 7.35 (m, 2H), 7.02 (m, 3H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 4.00 (s, 2H), 3.05 (d, 4H), 2.73 (m, 2H), 2.60 (m, 2H), 2.18 (m, 7H), 1.95 (s, 2H), 1.79 (m, 3H), 1.37 (m, 3H), 0.92 (s, 6H), 0.45 (m, 4H).

## Example 305

N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 305A

3-chloro-4-(((trans-4-hydroxycyclohexyl)methoxy)benzenesulfonamide

(Trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methanol (275 mg, prepared according to a procedures in WO 2008/124878) and 3-chloro-4-fluorobenzenesulfonamide (259 mg) in tetrahydrofuran (15 mL) were treated with sodium hydride (180 mg, 60%) overnight. The reaction was quenched with water (1 mL) and trifluoroacetic acid (4 mL) was added. The resulting mixture was stirred for 1 hour and concentrated. The residue was triturated with water and methanol to provide the title compound.

## Example 305B

N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 305A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.38 (s, 1H), 8.06 (d, 1H), 7.87 (d, 1H), 7.76 (dd, 1H), 7.57 (d, 1H), 7.51-7.55 (m, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.18 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.42 (dd, 1H), 6.18 (d, 1H), 4.54 (d, 1H), 3.91 (d, 2H), 3.07 (s, 4H), 2.75



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(s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.78-1.90 (m, 4H), 1.63-1.75 (m, 1H), 1.38 (t, 2H), 1.00-1.25 (m, 4H), 0.92 (s, 6H).

## Example 306

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 306A

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-chlorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide, (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride and Hunig's base for N<sup>1</sup>,N<sup>1</sup>,N<sup>2</sup>,N<sup>2</sup>-tetramethylethane-1,2-diamine in EXAMPLE 6A.

## Example 306B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 306A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.80 (s, 1H), 11.17 (brs, 1H), 8.09 (d, 1H), 7.71 (d, 1H), 7.63 (d, 1H), 7.58 (dd, 1H), 7.53 (dd, 1H), 7.50 (d, 1H), 7.34 (d, 2H), 7.03 (d, 2H), 6.74 (d, 1H), 6.66 (dd, 1H), 6.42 (m, 1H), 6.40 (t, 1H), 6.16 (d, 1H), 3.83 (m, 2H), 3.24 (m, 2H), 3.10 (m, 2H), 3.06 (br m, 4H), 2.72 (s, 2H), 2.17 (br m, 6H), 1.95 (s, 2H), 1.83 (m, 1H), 1.59 (br m, 2H), 1.38 (t, 2H), 1.20 (ddd, 2H), 0.92 (s, 6H).

## Example 307

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 307A

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethyl)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-(trifluoromethyl)benzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 307B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 307A for

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EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 8.78 (d, 1H), 8.58 (dd, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.43 (m, 2H), 7.16 (d, 1H), 7.06 (m, 2H), 6.74 (dd, 1H), 6.51 (m, 2H), 4.21 (d, 2H), 3.87 (m, 2H), 3.78 (td, 2H), 3.06 (m, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.13 (m, 4H), 1.95 (m, 6H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 308

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 308A

4-(3-(cyclopropylamino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 291C (4.14 g) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 2 hours. The mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of solvent gave the title compound.

## Example 308B

4-(3-(cyclopropyl(2,2,2-trifluoroethyl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (6 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (255 mg) and N,N-diisopropylethylamine (258 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of solvent gave the title compound.

## Example 308C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 308B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.38 (m, 1H), 8.55 (d, 2H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.05 (m, 3H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.07 (m, 4H), 2.82 (m, 4H), 2.18 (m, 7H), 1.38 (m, 2H), 0.92 (s, 6H), 0.44 (m, 4H).

## Example 309

N-[(3-chloro-4-({1-(oxetan-3-yl)piperidin-4-yl}methoxy)phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 294B (0.150 g) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL).

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After stirring for 1 hour the reaction was concentrated and dried under high vacuum. The residue was dissolved in dichloromethane (2 mL) and treated with sodium triacetoxyborohydride (0.050 g) and oxetan-3-one (0.017 g) and stirred overnight at room temperature. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (20 mL) and extracted into dichloromethane (50 mL). The organic layer was separated, washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.5% to 5% methanol/dichloromethane over 30 minutes (flow=40 mL/min) provided the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 11.21 (s, 1H), 8.05 (d, 1H), 7.87 (d, 1H), 7.75 (dd, 1H), 7.61-7.42 (m, 3H), 7.42-7.26 (m, 2H), 7.18 (d, 1H), 7.14-6.97 (m, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.51 (dt, 4H), 3.99 (d, 2H), 3.56-3.32 (m, 1H), 3.06 (s, 4H), 2.89-2.68 (m, 4H), 2.16 (d, 6H), 2.01-1.69 (m, 7H), 1.50-1.07 (m, 4H), 0.92 (s, 6H).

## Example 310

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 310A

3,5-difluoro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

EXAMPLE 37C (0.423 g) in tetrahydrofuran (30 mL) was treated with NaH (60% oil dispersion) (0.480 g), stirred 20 minutes at ambient temperature, treated with 3,4,5-trifluorobenzenesulfonamide (0.633 g) and stirred 30 minutes. N,N-Dimethylacetamide (15 mL) was added to increase solubility of the reactants and stirring was continued overnight at ambient temperature. Additional NaH (60% oil dispersion) (0.480 g) and N,N-dimethylacetamide (15 mL) were added and the mixture was heated overnight at 50° C. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl solution and then partitioned between saturated aqueous NH<sub>4</sub>Cl solution and ethyl acetate. The organic layer was washed with water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on amine functionalized silica gel with 0 to 2% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent. The residue was further purified by reverse phase HPLC on a C18 column using a gradient of 10-70% acetonitrile/0.1% trifluoroacetic acid in water to provide the title compound.

## Example 310B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 310A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>3</sub>) δ 13.06 (s, 1H), 8.41 (d, 1H), 8.11 (m, 2H), 8.08 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 4.26 (d, 2H), 3.85 (dd, 1H), 3.83

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(dd, 1H), 3.74 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.87 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 311

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([3-(cyclopropyl(oxetan-3-yl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 311A

4-(3-(cyclopropyl(oxetan-3-yl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (5 mL) was added oxetan-3-one (72 mg) followed by sodium triacetoxyborohydride (318 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, evaporation of the solvent gave the crude title compound.

## Example 311B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([3-(cyclopropyl(oxetan-3-yl)amino]propyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 311A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 11.37 (s, 1H), 8.68 (s, 1H), 8.54 (d, 1H), 8.02 (d, 1H), 7.79 (d, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 4.62 (m, 2H), 4.48 (t, 2H), 3.98 (m, 1H), 3.37 (m, 2H), 3.06 (m, 4H), 2.73 (d, 2H), 2.59 (m, 2H), 2.23 (m, 6H), 1.95 (s, 2H), 1.74 (m, 3H), 1.38 (t, 2H), 0.92 (s, 6H), 0.41 (m, 4H).

## Example 312

N-[(3-chloro-4-([1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy)phenyl)sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To EXAMPLE 294B (0.065 g) was added hydrogen chloride (4.0M in dioxane, 0.339 mL) and a few drops of methanol. After 30 minutes, the reaction was concentrated, and (S)-1-methylpyrrolidine-2-carboxylic acid (0.013 g), N<sup>1</sup>-((ethylimino)methylene)-N<sup>3</sup>,N<sup>3</sup>-dimethylpropane-1,3-diamine hydrochloride (0.026 g), suspended in dichloromethane (0.5 mL) were added followed by diisopropylethylamine (0.036 mL). The mixture stirred at room temperature. After stirring overnight, the reaction mixture was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 1% to 10% methanol (containing 1N NH<sub>3</sub>)/dichloromethane over 30 minutes (flow=40 mL/minutes) to provide the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.51 (s, 1H), 10.00-9.22 (m, 1H), 7.92 (d, 1H), 7.68 (d, 1H), 7.57 (d, 1H), 7.47 (dd, 1H), 7.44-7.38 (m, 1H), 7.38-7.31 (m, 2H), 7.29 (d, 1H), 7.12-7.01 (m,

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2H), 6.90 (d, 1H), 6.61 (dd, 1H), 6.31 (dd, 1H), 6.25 (d, 1H), 5.85 (d, 1H), 4.40 (s, 1H), 3.92 (s, 4H), 3.17-2.89 (m, 8H), 2.73 (s, 4H), 2.38 (s, 3H), 2.18 (m, 6H), 1.96 (s, 2H), 1.80 (m, 2H), 1.57 (s, 2H), 1.39 (s, 2H), 1.22 (m, 2H), 0.96 (m, 6H).

**Example 313**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 313A**

3,4-difluoro-5-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was obtained as a side product in EXAMPLE 310A.

**Example 313B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 313A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.98 (m, 2H), 7.66 (m, 1H), 7.63 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.77 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.12 (d, 2H), 3.83 (m, 2H), 3.75 (m, 2H), 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.82 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 314**

N-[(5-chloro-6-[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 314A**

(S)-5-chloro-6-((4-cyclopropylmorpholin-2-yl)methoxy)pyridine-3-sulfonamide

A solution of EXAMPLE 244B (250 mg), anhydrous methanol (6 mL), (1-ethoxycyclopropoxy)trimethylsilane (0.474 mL), and acetic acid (0.509 mL) was heated at 70° C. for 30 minutes. After cooling to ambient temperature, sodium cyanoborohydride (112 mg) was added and the mixture was stirred for 18 hours. Additional sodium cyanoborohydride (75 mg) was added and stirring was continued 18 hours. The reaction was concentrated and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The crude product was isolated from the dried methylene chloride layer and was purified on silica gel and was eluted with a 1, 2.5, 5, 10% methanol in methylene chloride step gradient to provide the title compound.

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N-[(5-chloro-6-[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 314A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 12.98 (s, 1H), 9.09 (d, 1H), 8.69 (d, 1H), 8.41 (d, 1H), 8.11 (d, 1H), 7.66-7.64 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (m, 1H), 6.48 (m, 1H), 5.72 (br s, 1H), 4.62-4.57 (m, 1H), 4.51-4.47 (m, 1H), 3.99 (m, 1H), 3.85 (m, 1H), 3.57 (m, 1H), 3.08-3.01 (m, 5H), 2.77 (s, 2H), 2.69 (m, 1H), 2.39-2.24 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.57 (m, 1H), 1.39 (t, 2H), 0.94 (m, 6H), 0.48-0.3 (m, 4H).

**Example 315**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 11.35 (br s, 1H), 8.61 (m, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.82 (dd, 1H), 7.45-7.57 (m, 3H), 7.33 (d, 2H), 7.15 (d, 1H), 7.01 (d, 2H), 6.65 (dd, 1H), 6.40 (dd, 1H), 6.11 (d, 1H), 3.85 (dd, 2H), 3.53 (m, 2H), 3.27 (m, 4H), 2.63 (m, 2H), 2.04 (m, 2H), 1.91 (s, 2H), 1.77 (m, 2H), 1.62 (m, 4H), 1.45 (m, 2H), 1.38 (m, 2H), 1.27 (m, 1H), 1.23 (m, 4H), 0.92 (s, 6H).

**Example 316**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 316A**

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting (tetrahydro-2H-pyran-4-yl)methanol for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

**Example 316B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 316A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.77 (s, 1H), 11.35 (br s, 1H), 8.06 (m, 1H), 7.88 (d, 1H), 7.79 (dd, 1H), 7.58 (s, 1H), 7.53 (t, 1H), 7.46 (d, 1H), 7.34 (d, 2H), 7.22 (d, 1H), 7.01 (d, 2H), 6.66 (dd,

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1H), 6.42 (dd, 1H), 6.11 (d, 1H), 3.99 (d, 2H), 3.88 (dd, 2H), 3.52 (m, 2H), 3.34 (m, 4H), 2.62 (m, 2H), 2.04 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.46 (m, 2H), 1.38 (m, 4H), 0.92 (s, 6H), 0.75 (m, 2H).

## Example 317

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate

## Example 317A

methyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting methyl chloroformate for methyl iodide in EXAMPLE 134B.

## Example 317B

methyl 2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 317A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.84 (t, 1H), 8.43 (d, 1H), 8.35 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (bs, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.29-4.03 (m, 1H), 3.89-3.70 (m, 3H), 3.71 (s, 3H), 3.55-3.38 (m, 3H), 3.07 (m, 4H), 2.96 (dt, 1H), 2.86 (dd, 1H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 318

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

## Example 318A

N-ethyl-N-methyl-2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxamide

The title compound was prepared by substituting N-methyl-N-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

## Example 318B

2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 318A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26

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(d, 1H), 8.86 (t, 1H), 8.44 (d, 1H), 8.33 (dd, 1H), 8.12 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.92-3.85 (m, 2H), 3.75 (d, 1H), 3.62 (dt, 1H), 3.55-3.48 (m, 1H), 3.45-3.39 (m, 2H), 3.21 (q, 2H), 3.07 (m, 4H), 2.99 (dt, 1H), 2.90 (dd, 1H), 2.77 (s, 2H), 2.76 (s, 3H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.06 (t, 3H), 0.93 (s, 6H).

## Example 319

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(methylsulfonyl)morpholin-2-yl]methyl}amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 319A

4-((4-(methylsulfonyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting methanesulfonyl chloride for methyl iodide in EXAMPLE 134B.

## Example 319B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(methylsulfonyl)morpholin-2-yl]methyl}amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 319A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.25 (d, 1H), 8.84 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.13 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.99 (m, 1H), 3.92-3.88 (m, 2H), 3.64 (m, 2H), 3.56 (m, 1H), 3.50 (m, 1H), 3.07 (m, 4H), 3.04 (s, 3H), 2.95-2.88 (m, 2H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 320

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[3-(cyclobutyl(cyclopropyl)amino)propyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 320A

4-(3-(cyclobutyl(cyclopropyl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (5 mL) was added cyclobutanone (70 mg) followed by sodium triacetoxyborohydride (318 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous



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NaHCO<sub>3</sub>, water and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, evaporation of solvent gave the title compound.

**Example 320B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclobutyl(cyclopropyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 320A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.70 (m, 1H), 8.54 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.37 (q, 2H), 3.06 (m, 4H), 2.73 (s, 2H), 2.63 (m, 2H), 2.21 (m, 8H), 1.82 (m, 3H), 1.53 (m, 2H), 1.38 (t, 2H), 0.94 (m, 6H), 0.41 (m, 4H).

**Example 321**

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 321A**

ethyl 5,5-difluoro-2-oxocyclohexanecarboxylate

To a solution of diethyl 4,4-difluoroheptanedioate (4.3 g) in toluene (50 mL) was added potassium 2-methylpropan-2-olate (2.87 g) and the reaction stirred overnight at room temperature. The reaction was quenched with 1N aqueous HCl (100 mL) and extracted with diethyl ether (150 mL). The ether layer was washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 5% ethyl acetate/hexanes gave the title compound.

**Example 321B**

ethyl 5,5-difluoro-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a solution of EXAMPLE 321A (2.37 g) in dichloromethane (40 mL) at 0° C. was added N,N-diisopropylethylamine (5.02 mL) followed by trifluoromethanesulfonic anhydride (2.33 mL) and the reaction was allowed to slowly warm to room temperature. After stirring overnight the reaction was quenched with 10 mL of water then 1N aqueous HCl (100 mL). The reaction was extracted with dichloromethane (3×75 mL), and the combined organics were washed with brine (50 mL) and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 25% ethyl acetate/hexanes gave the title compound.

**Example 321C**

ethyl 2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarboxylate

A solution of EXAMPLE 321B (3.47 g), 4-chlorophenylboronic acid (1.925 g) and cesium fluoride (3.43 g) in 30 mL

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of 1,2-dimethoxyethane and 15 mL of ethanol was degassed with nitrogen for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.237 g) was added and the reaction was heated to 70° C. The reaction was diluted with ether (200 mL) and washed with 1N aqueous HCl (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 8% ethyl acetate/hexanes over 40 minutes gave the title compound.

**Example 321D**

(2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methanol

To a solution of EXAMPLE 321C (1.84 g) in diethyl ether (25 mL) at 0° C. was added lithium aluminum hydride (1.0M, 4.28 mL). The reaction was quenched with the dropwise addition of water, then 1N aqueous HCl (50 mL) was added and the reaction diluted with diethyl ether (100 mL). The organic layer was separated, washed with brine (50 mL) dried over magnesium sulfate, filtered and concentrated to provide the title compound.

**Example 321E**

2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarbaldehyde

To a solution of EXAMPLE 321D (1.38 g) in dichloromethane (25 mL) was added Dess-Martin periodinane (2.489 g) and the reaction stirred for 1 hour at room temperature. The reaction was quenched with 1N aqueous NaOH solution (75 mL) and the product was extracted into dichloromethane (2×100 mL). The combined organics were washed with brine (75 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveris 80 g) eluting with a gradient of 1% to 10% ethyl acetate/hexanes over 40 minutes gave the title compound.

**Example 321F**

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 321E for EXAMPLE 15E in EXAMPLE 15G.

**Example 321G**

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 321F for EXAMPLE 15G in EXAMPLE 15H.

**Example 321H**

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 321G for EXAMPLE 1E and EXAMPLE 3J for

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EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.74-11.63 (m, 1H), 11.53-11.29 (m, 1H), 8.57 (d, 2H), 8.05 (d, 1H), 7.85-7.77 (m, 1H), 7.49 (d, 3H), 7.38 (d, 2H), 7.16-7.06 (m, 3H), 6.73-6.64 (m, 1H), 6.43-6.36 (m, 1H), 6.21-6.14 (m, 1H), 3.93-3.77 (m, 2H), 3.29 (d, 4H), 3.07 (s, 4H), 2.79-2.57 (m, 4H), 2.45 (dd, 2H), 2.19 (s, 6H), 1.99-1.80 (m, 1H), 1.70-1.54 (m, 2H), 1.38-1.13 (m, 2H).

## Example 322

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 322A

## tert-butyl

4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (2 g) was taken up in tetrahydrofuran (20 mL) and cooled in an ice bath. Lithium aluminum hydride (1.0M in dioxane, 5.09 mL) was added dropwise. The reaction was stirred at room temperature for 2 hours. The reaction was quenched with water and with 1M aqueous NaOH solution and then stirred another 1 hour at room temperature. The mixture was extracted with ethyl acetate, and the extracts were combined and washed with water and with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The crude product was used without further purification.

## Example 322B

tert-butyl 4-((2-chloro-4-sulfamoylphenoxy)methyl)-4-fluoropiperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 322A for (tetrahydro-2H-pyran-4-yl)methanol and 3-chloro-4-fluorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 322C

3-chloro-4-((4-fluoropiperidin-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 322B for EXAMPLE 1A in EXAMPLE 1B.

## Example 322D

3-chloro-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 322C (830 mg) in tetrahydrofuran (15 mL) and acetic acid (5 mL) was added oxetan-3-one (163 mg) and MP-cyanoborohydride (2.38 mmol/g, 1.9 g).

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The mixture was stirred at room temperature overnight. The reaction was then filtered and the filtrate was concentrated under vacuum. The residue was slurried in ether and the solid product was collected by filtration.

## Example 322E

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 322D for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 8.06 (d, 1H), 7.89 (d, 1H), 7.79 (m, 1H), 7.58 (d, 1H), 7.52 (t, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.42 (m, 1H), 6.18 (d, 1H), 4.55 (t, 2H), 4.44 (t, 2H), 4.24 (d, 2H), 3.44 (m, 2H), 3.07 (br s, 4H), 2.74 (m, 2H), 2.59 (m, 2H), 2.14 (m, 7H), 1.95 (m, 4H), 1.78 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 323

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro furan-3-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 323A

3-chloro-4-((tetrahydrofuran-3-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-chlorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydrofuran-3-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A, except here, dimethylformamide was used in place of tetrahydrofuran and the reaction was heated at 70° C. for two days.

## Example 323B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydro furan-3-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 323A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.73 (s, 1H), 8.07 (d, 1H), 7.89 (d, 1H), 7.80 (dd, 1H), 7.59 (d, 1H), 7.51 (dd, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.23 (d, 1H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.42 (m, 1H), 6.19 (d, 1H), 4.07 (m, 2H), 3.80 (m, 2H), 3.68 (m, 1H) 3.56 (m, 1H), 3.10 (br m, 4H), 2.85 (br s, 2H), 2.69 (m, 1H), 2.32 (br m, 4H), 2.17 (br m, 2H), 2.02 (m, 1H), 1.96 (s, 2H), 1.69 (m, 1H), 1.40 (t, 2H), 0.92 (s, 6H).

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## Example 324

4-(4-([2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 324A

4-((trans-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 120A for EXAMPLE 39B in EXAMPLE 39C.

## Example 324B

4-(4-([2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 321G for EXAMPLE 1E and EXAMPLE 324A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.65-8.50 (m, 2H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.60-7.44 (m, 3H), 7.41-7.34 (m, 2H), 7.14-7.02 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.17 (d, 1H), 4.50 (d, 1H), 3.23 (t, 2H), 3.06 (s, 4H), 2.70 (d, 4H), 2.44 (s, 2H), 2.33-1.94 (m, 6H), 1.78 (dd, 4H), 1.51 (d, 2H), 1.23 (s, 2H), 1.16-0.92 (m, 2H).

## Example 325

N-([3-chloro-4-([4-fluorotetrahydro-2H-pyran-4-yl]methoxy)phenyl]sulfonyl)-4-([9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 325A

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 265G.

## Example 325B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 325A for EXAMPLE 15G in EXAMPLE 15H.

## Example 325C

N-([3-chloro-4-([4-fluorotetrahydro-2H-pyran-4-yl]methoxy)phenyl]sulfonyl)-4-([9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 325B for EXAMPLE 1E and EXAMPLE 286A

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for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.13 (s, 1H), 8.05 (d, 1H), 7.87 (d, 1H), 7.80-7.70 (m, 1H), 7.59-7.46 (m, 3H), 7.34 (d, 2H), 7.21 (d, 1H), 7.11-7.03 (m, 2H), 6.66 (d, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.50 (dd, 4H), 4.26 (d, 2H), 3.85-3.69 (m, 2H), 3.61 (d, 3H), 3.05 (s, 4H), 2.69 (s, 2H), 2.37 (s, 4H), 2.17 (s, 6H), 2.04 (s, 2H), 1.87 (d, 4H), 1.49 (d, 6H).

## Example 326

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 326A

(R)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258E for EXAMPLE 173A in EXAMPLE 173B.

## Example 326B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 326A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

## Example 327

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 327A

(S)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259E for EXAMPLE 173A in EXAMPLE 173B.

## Example 327B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 327A for EXAMPLE 130C in EXAMPLE

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130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

Example 328

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 328A

spiro[2.5]octan-5-one

To a solution of 3-ethoxycyclohex-2-enone (48.1 mL) in ether (1000 mL) was added titanium(IV) isopropoxide (110 mL) followed by addition of ethylmagnesium bromide (357 mL) at ambient temperature. The reaction mixture was stirred for 2 hours at ambient temperature and was then quenched with water (500 mL). The organic layer was separated (decanted) and the water layer was extracted with ether (3×300 mL). The combined extracts were partially concentrated to approximately 300 mL. *p*-Toluenesulfonic acid monohydrate (3.0 g) was added and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then washed with saturated aqueous NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was purified by fractional distillation (1st fraction b.p. 27° C. at 23 torr (not product), 2nd fraction (product) b.p. 75° C. at 8 torr).

Example 328B

5-chlorospiro[2.5]oct-5-ene-6-carbaldehyde

N,N-dimethylformamide (2.1 mL) in dichloromethane (3.2 mL) at -5° C. was treated slowly with POCl<sub>3</sub> (2.33 mL) keeping the bath temperature less than 0° C. The cooling bath was removed and the mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was returned to the cooling bath and EXAMPLE 328A (2.484 g) in dichloromethane (4 mL) was added slowly to the reaction mixture. The reaction mixture was heated at 45° C. for 15 hours, cooled to room temperature and then poured into a mixture of ice and saturated aqueous sodium acetate solution. After the ice melted, the mixture was extracted with diethyl ether. The combined extracts were washed with saturated aqueous NaHCO<sub>3</sub> solution and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed with 0 to 10% CH<sub>2</sub>Cl<sub>2</sub> in hexanes, then 25% CH<sub>2</sub>Cl<sub>2</sub> in hexanes and then 100% CH<sub>2</sub>Cl<sub>2</sub> as the eluents.

Example 328C

5-(4-chlorophenyl)spiro[2.5]oct-5-ene-6-carbaldehyde

EXAMPLE 328B (2.9 g), 4-chlorophenylboronic acid (2.87 g), palladium(II) acetate (0.103 g), K<sub>2</sub>CO<sub>3</sub> (5.28 g) and tetrabutylammonium bromide (4.93 g) were combined in a 100-mL round bottomed flask with water (17.0 mL). The flask was flushed with nitrogen and stirred at 45° C. for 14

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hours. The reaction mixture was partitioned between brine and diethyl ether. The organic layer was washed with brine, dried (MgSO<sub>4</sub>), filtered through a plug of celite, concentrated and chromatographed on silica gel with 0 to 2% ethyl acetate in hexanes as the eluent.

Example 328D

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 15F for tert-butyl piperazine carboxylate and EXAMPLE 328C for 4-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

Example 328E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl)piperazin-1-yl)benzoic acid hydrochloride

EXAMPLE 328D (0.85 g) in a mixture of tetrahydrofuran (4.8 mL), methanol (2.4 mL) and water (2.4 mL) was treated with LiOH·H<sub>2</sub>O (0.184 g) and heated overnight at 50° C. The reaction mixture was cooled to room temperature, concentrated to remove tetrahydrofuran and methanol and acidified with 1 N aqueous HCl causing precipitation of the product. The solid was collected by filtration, rinsed with water and dried overnight in a vacuum oven at 80° C. to provide the title compound.

Example 328F

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.32 (d, 1H), 8.68 (t, 1H), 8.44 (d, 1H), 8.38 (dd, 1H), 8.10 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.43 (m, 2H), 7.10 (m, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.51 (m, 2H), 3.97 (dd, 2H), 3.30 (td, 2H), 3.16 (t, 2H), 3.06 (m, 4H), 2.81 (s, 2H), 2.37 (t, 2H), 2.16 (m, 4H), 2.11 (s, 2H), 1.81 (m, 1H), 1.58 (dd, 2H), 1.45 (t, 2H), 1.32 (qd, 2H), 0.38 (s, 4H).

Example 329

N-{[5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 329A

ethyl 4-(cyclopropylamino)cyclohexanecarboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (3.4 g) in dichloromethane (30 mL) was added cyclopropanamine (1.14 g) followed by sodium triacetoxymethylborohydride (4.24 g). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with 2N NaOH,



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water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 329B

ethyl 4-(cyclopropyl(oxetan-3-yl)amino)cyclohexanecarboxylate

To a solution of EXAMPLE 329A (1.05 g) in dichloromethane (10 mL) was added oxetan-3-one (0.358 g) followed by sodium triacetoxyborohydride (1.05 g). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with 2N aqueous NaOH, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 329C

(4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl) methanol

To a solution of EXAMPLE 329B (1.2 g) in tetrahydrofuran (20 mL) was added lithium aluminum hydride (0.681 g). The mixture was stirred overnight. 2N aqueous NaOH solution was added dropwise to the reaction mixture. The mixture was then diluted with ethyl acetate (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 329D

5-chloro-6-((4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 329C (706 mg) in N,N-dimethylformamide (6 mL) was added NaH (60% in mineral oil, 300 mg). The mixture was stirred for 30 minutes, and then 5,6-dichloropyridine-3-sulfonamide (706 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent the residue was loaded on a silica gel cartridge and eluted with 5 to 10% 7N NH<sub>3</sub> in methanol in dichloromethane to provide the title compound.

## Example 329E

N-([5-chloro-6-((4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 329D for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.50 (m, 1H), 8.16 (s, 1H), 8.02 (d, 1H), 7.51 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.21 (s, 1H), 4.70 (m, 2H), 4.43 (t, 3H), 4.19 (m, 2H), 3.12 (m, 4H), 2.84 (m, 2H), 2.19 (m, 6H), 1.96 (s, 3H), 1.77 (m, 3H), 1.38 (m, 7H), 0.93 (s, 6H), 0.44 (m, 4H).

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## Example 330

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J and EXAMPLE 218A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.42 (m, 2H), 7.09 (m, 2H), 6.95 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 3.84 (m, 2H), 3.58 (td, 1H), 3.45 (m, 2H), 3.06 (m, 4H), 2.93 (d, 1H), 2.81 (s, 2H), 2.69 (d, 1H), 2.35 (m, 3H), 2.19 (m, 5H), 2.11 (s, 2H), 1.58 (m, 1H), 1.45 (t, 2H), 0.42 (m, 8H).

## Example 331

N-([3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 331A

tert-butyl 2-((2-chloro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

To a solution of tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (0.478 g) in anhydrous N,N-dimethylformamide (5 mL) was added sodium hydride (0.280 g). The mixture was stirred at room temperature for 30 minutes, followed by addition of 3-chloro-4-fluorobenzenesulfonamide (0.419 g). The mixture was stirred at 40° C. overnight. The reaction was quenched with water (10 mL), and the mixture was adjusted to ~pH 7 and extracted with ethyl acetate. The crude product was purified on a silica gel column eluting with 60% ethyl acetate in hexane to provide the title compound.

## Example 331B

3-chloro-4-(morpholin-2-ylmethoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 331A for EXAMPLE 113A in EXAMPLE 134A.

## Example 331C

3-chloro-4-((4-(cyclopropylmorpholin-2-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 331B for EXAMPLE 173A in EXAMPLE 173B.

## Example 331D

N-([3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 331C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 8.27 (dd, 1H), 8.09 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.05 (d, 1H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.50 (m, 1H), 4.20 (dd, 1H), 4.10 (dd, 1H), 3.94 (m, 1H), 3.86 (d, 1H), 3.58 (dt, 1H), 3.06 (m, 5H), 2.77 (s, 2H), 2.69 (d, 1H), 2.40-2.20 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.60 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.41 (m, 4H).

## Example 332

N-[(3-chloro-4-[[4-(4-cyclopropylmorpholin-2-yl)methyl]amino]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 332A

tert-butyl 2-((2-chloro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

A solution of 3-chloro-4-fluorobenzenesulfonamide (1.0 g), tert-butyl 2-(aminomethyl)morpholine-4-carboxylate (1.135 g) and N-ethyl-N-isopropylpropan-2-amine (1.246 mL) in dimethylsulfoxide (15 mL) was stirred at 115° C. for 72 hours. The mixture was concentrated, and the residue was purified on a silica gel column eluting with 60% ethyl acetate to provide the title compound.

## Example 332B

3-chloro-4-(morpholin-2-ylmethylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 332A for EXAMPLE 113A in EXAMPLE 134A.

## Example 332C

The title compound was prepared by substituting EXAMPLE 332B for EXAMPLE 173A in EXAMPLE 173B.

## Example 332D

N-[(3-chloro-4-[[4-(4-cyclopropylmorpholin-2-yl)methyl]amino]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 332C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 8.45 (m, 2H), 8.21 (dd, 1H), 8.12 (d, 1H), 7.69 (d, 1H), 7.67 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.78 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (m, 1H), 6.37 (m, 1H), 3.84 (d, 1H), 3.77 (m, 1H), 3.54 (dt, 1H), 3.35 (m, 2H), 3.05 (m, 4H), 2.94 (d, 1H), 2.77 (s, 2H), 2.68 (d, 1H), 2.32 (dt, 1H), 2.26 (m, 2H), 2.18-2.12 (m, 5H), 1.97 (s, 2H), 1.55 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.41 (m, 4H).

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## Example 333

2-[[2-(chloro-4-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

## Example 333A

2-((2-chloro-4-sulfamoylphenylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 332B for EXAMPLE 134A and N-methyl-N-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

## Example 333B

2-[[2-(chloro-4-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 333A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 8.46 (s, 1H), 8.45 (s, 1H), 8.20 (dd, 1H), 8.10 (d, 1H), 7.69 (d, 1H), 7.67 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.79 (d, 1H), 6.73 (dd, 1H), 6.52 (dd, 1H), 6.49 (d, 1H), 6.43 (m, 1H), 3.83 (d, 2H), 3.73 (d, 1H), 3.59 (dt, 1H), 3.41-3.35 (m, 3H), 3.20 (q, 2H), 3.05 (m, 4H), 2.95 (t, 1H), 2.84 (dd, 1H), 2.76 (s, 2H), 2.73 (s, 3H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.04 (t, 3H), 0.94 (s, 6H).

## Example 334

(2S)-2-[[2-(3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

## Example 334A

(S)-2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and N-methyl-N-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

## Example 334B

(2S)-2-[[2-(3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 334A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.98 (s, 1H), 9.08 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.67 (t, 1H),

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7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.58 (dd, 1H), 4.47 (dd, 1H), 4.03 (m, 1H), 3.84 (m, 2H), 3.63 (dt, 1H), 3.45 (d, 1H), 3.22 (q, 2H), 3.07 (m, 4H), 3.05-2.95 (m, 2H), 2.78 (s, 3H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.07 (t, 3H), 0.94 (s, 6H).

**Example 335**

N-[(5-chloro-6-[[4-(4-cyclopropylmorpholin-2-yl)methyl]amino]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 335A**

tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-ylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 335B**

5-chloro-6-(morpholin-2-ylmethylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 335A for EXAMPLE 113A in EXAMPLE 134A.

**Example 335C**

5-chloro-6-((4-cyclopropylmorpholin-2-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 335B for EXAMPLE 173A in EXAMPLE 173B.

**Example 335D**

N-[(5-chloro-6-[[4-(4-cyclopropylmorpholin-2-yl)methyl]amino]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 335C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (s, 1H), 9.15 (d, 1H), 8.49 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.80 (t, 1H), 7.69 (d, 1H), 7.65 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.73 (dd, 1H), 6.52 (m, 1H), 6.49 (d, 1H), 3.92 (m, 1H), 3.84 (m, 2H), 3.70 (m, 1H), 3.54 (dt, 1H), 3.05 (m, 4H), 2.99 (d, 1H), 2.76 (s, 2H), 2.68 (d, 1H), 2.32 (dt, 1H), 2.25 (m, 2H), 2.12 (m, 5H), 1.97 (s, 2H), 1.53 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H), 0.40 (m, 4H).

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2-[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

**Example 336A**

2-((3-chloro-5-sulfamoylpyridin-2-ylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 335B for EXAMPLE 134A and N-methyl-N-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

**Example 336B**

2-[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 336A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.14 (d, 1H), 8.51 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.89 (m, 1H), 7.69 (d, 1H), 7.66 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.74 (dd, 1H), 6.51 (m, 1H), 6.48 (d, 1H), 3.96 (m, 1H), 3.90-3.70 (m, 4H), 3.59 (dt, 1H), 3.43 (d, 1H), 3.17 (q, 2H), 3.05 (m, 4H), 2.95 (dt, 1H), 2.81 (dd, 1H), 2.76 (s, 2H), 2.72 (s, 3H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.03 (t, 3H), 0.93 (s, 6H).

**Example 337**

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[trans-4-hydroxy-4-methylcyclohexyl]methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 337A**

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

**Example 337B**

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 337A (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL)

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were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

## Example 337C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)  
methanol

To a mixture of LiBH<sub>4</sub> (13 g), EXAMPLE 337B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

## Example 337D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 337C (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 337E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 337D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the product.

## Example 337F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 337G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 337F (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL).

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After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M aqueous NaOH (69 mL) was added, followed by 30% aqueous H<sub>2</sub>O<sub>2</sub> (8.43 mL), and the solution was stirred for 1 hour. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH<sub>2</sub>PO<sub>4</sub>. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 337H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 337G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 337I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 337H (1.55 g), EXAMPLE 337E (2.42 g), and HK<sub>3</sub>PO<sub>4</sub> (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed three times with 1M aqueous NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 337J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 337I (200 mg) in dioxane (10 mL) and 1M aqueous NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 337K

tert-butyl  
(4-hydroxy-4-methylcyclohexyl)methylcarbamate

To a vigorous stirring solution of tert-butyl (4-oxocyclohexyl)methylcarbamate (1.7 g) in tetrahydrofuran (40 mL) at -78° C. was dropwise added 1.6 M methylolithium (14.02 mL) in ether. After completion of the addition, the mixture was stirred at -78° C. for 1.2 hours and poured into a cold NH<sub>4</sub>Cl aqueous solution. The resulting mixture was extracted with dichloromethane (100 mL, three times) and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The resi-



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due was dissolved in dichloromethane and loaded onto an Analogix purification system, and it was eluted with 0-50% ethyl acetate in dichloromethane to provide the title compound.

## Example 337L

## 4-(aminomethyl)-1-methylcyclohexanol

EXAMPLE 337K (1.3 g) in dichloromethane (5 mL) at 0° C. was treated with trifluoroacetic acid (2.1 mL) and a few drops of water for 1 hour. The reaction mixture was concentrated and the residue was directly used for next step.

## Example 337M

## 4-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 337L (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 mL) was treated with triethylamine overnight. The reaction mixture, was concentrated and the residue was purified by a reverse phase chromatography, eluting with 30%-50% acetonitrile in 0.1% trifluoroacetic acid water solution to isolate the title compound.

## Example 337N

## 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A mixture of EXAMPLE 337J (3.0 g), EXAMPLE 337M (1.98 g), N,N-dimethylpyridin-4-amine (1.93 g) and N<sup>1</sup>-((ethylimino)methylene)-N<sup>3</sup>,N<sup>3</sup>-dimethylpropane-1,3-diamine hydrochloride (1.31 g) in dichloromethane (50 mL) was stirred overnight and concentrated. The residue was purified by reverse chromatography, eluted with 40%-70% acetonitrile in 0.1% TFA water. The desired fractions were concentrated to remove acetonitrile, neutralized with NaHCO<sub>3</sub> and extracted with dichloromethane. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and dried to provide the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.52-8.58 (m, 2H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.53 (d, 1H), 7.47-7.52 (m, 2H), 7.30-7.37 (m, 2H), 7.07 (d, 1H), 7.01-7.06 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.25 (s, 1H), 3.25-3.32 (m, 4H), 3.07 (s, 4H), 2.75 (s, 2H), 2.09-2.24 (m, 6H), 1.95 (s, 2H), 1.50-1.73 (m, 5H), 1.28-1.43 (m, 4H), 1.06-1.18 (m, 5H), 0.92 (s, 6H).

## Example 338

## 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 338A

## methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycar-

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bonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

## Example 338B

## methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 338A (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

## Example 338C

## (2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH<sub>4</sub> (13 g), EXAMPLE 338B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N aqueous HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

## Example 338D

## tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 338C (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 338E

## 1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 338D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 338F

## 5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hex-

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amethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 338G

## 1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 338F (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M aqueous NaOH (69 mL) was added, followed by 30% aqueous H<sub>2</sub>O<sub>2</sub> (8.43 mL), and the solution was stirred for 1 hour. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH<sub>2</sub>PO<sub>4</sub>. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 338H

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 338G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 338I

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-ylbenzoate

A mixture of EXAMPLE 338H (1.55 g), EXAMPLE 338E (2.42 g), and HK<sub>2</sub>PO<sub>4</sub> (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed three times with 1M aqueous NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 338J

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-ylbenzoic acid

EXAMPLE 338I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three

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times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 338K

tert-butyl  
(4-hydroxy-4-methylcyclohexyl)methylcarbamate

To a vigorous stirring solution of tert-butyl (4-oxocyclohexyl)methylcarbamate (1.7 g) in tetrahydrofuran (40 mL) at -78° C. was dropwise added 1.6 M methylolithium (14.02 mL) in ether. After completion of the addition, the mixture was stirred at -78° C. for 1.2 hours and poured into a cold NH<sub>4</sub>Cl aqueous solution. The resulting mixture was extracted with dichloromethane (100 mL, three times) and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was dissolved in dichloromethane and loaded onto an Analogix purification system, and it was eluted with 0-50% ethyl acetate in dichloromethane to provide the title compound.

## Example 338L

## 4-(aminomethyl)-1-methylcyclohexanol

EXAMPLE 338K (1.3 g) in dichloromethane (5 mL) at 0° C. was treated with trifluoroacetic acid (2.1 mL) and a few drops of water for 1 hour. The reaction mixture was concentrated and the residue was directly used for next step.

## Example 338M

## 4-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 338L (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 mL) was treated with triethylamine overnight. The reaction mixture was concentrated and the residue was purified by a reverse phase chromatography, eluting with 30%-50% acetonitrile in 0.1% trifluoroacetic acid water solution to isolate the title compound.

## Example 338N

## 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((cis-4-hydroxy-4-methylcyclohexyl)methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A mixture of EXAMPLE 338J (144 mg), EXAMPLE 338M (95 mg), N,N-dimethylpyridin-4-amine (123 mg) and N<sup>1</sup>-((ethylimino)methylene)-N<sup>3</sup>,N<sup>3</sup>-dimethylpropane-1,3-diamine hydrochloride (62.7 mg) in dichloromethane (7 mL) was stirred overnight and concentrated. The residue was purified by reverse chromatography, eluted with 40%-70% acetonitrile in 0.1% TFA water. The desired fractions were concentrated, neutralized with NaHCO<sub>3</sub> and extracted with dichloromethane. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and dried to provide the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.59 (t, 1H), 8.55 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.54 (d, 1H), 7.46-7.52 (m, 2H), 7.30-7.38 (m, 2H), 7.00-7.10 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H),

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3.95 (s, 1H), 3.25 (t, 4H), 3.07 (s, 4H), 2.75 (s, 2H), 2.10-2.26 (m, 6H), 1.95 (s, 2H), 1.29-1.62 (m, 8H), 1.16-1.30 (m, 2H), 1.08 (s, 3H), 0.92 (s, 6H).

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N-[(5-chloro-6-[[[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 339A

(1R,4S)-methyl spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-carboxylate

A reaction mixture of 1,4-dioxaspiro[4.4]non-6-ene (5 g), methyl acrylate (10.24 g), and hydroquinone (0.13 g) was heated at 100° C. in acetonitrile (12 mL) for three days. After cooling, the solvent was removed, and residue was purified by flash chromatography on silica gel eluting with 4:1 hexane/ethyl acetate to provide the title compound as a mixture of two isomers.

## Example 339B

(1R,4S)-spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-ylmethanol

EXAMPLE 339A (1.0 g) in tetrahydrofuran was cooled to 0° C. To this solution was added 1.0 N lithium aluminum hydride (2.8 mL) dropwise. The reaction mixture was stirred for 2 hours. Water (0.4 mL) was added followed by 2 N aqueous NaOH (0.2 mL). The solid was filtered off, and the filtrate was concentrated. Toluene was added, and it was then distilled to remove any trace amount of water. The title compound was used for the next reaction without further purification.

## Example 339C

5-chloro-6-(((1S,2R,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 339B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B. The two stereoisomers at the 5 position were isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 $\mu$ , C18(2), 250 $\times$ 21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% trifluoroacetic acid. The desired fractions were collected, and the solvents were removed under reduced vacuum at 60° C. During this process, a lot of solid formed. It was then partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give the title compound.

## Example 339D

5-chloro-6-(((1S,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 339C (0.44 g) in tetrahydrofuran (15 mL) was treated with 3.0 M methylmagnesium bromide (5.3 mL) at 0°

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C. The solution was stirred for 16 hours. The reaction mixture was then partitioned between ethyl acetate and 0.05 N aqueous HCl (20 mL). The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

## Example 339E

N-[(5-chloro-6-[[[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 339D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>)  $\delta$  11.66 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 8.02 (d, 1H), 7.49-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.20 (s, 1H), 4.40-4.48 (m, 2H), 4.31 (s, 1H), 3.09 (s, 4H), 2.83 (s, 2H), 2.15-2.33 (m, 7H), 1.96 (s, 2H), 1.87 (d, 1H), 1.65-1.69 (m, 1H), 1.54-1.56 (m, 2H), 1.36-1.47 (m, 6H), 1.26-1.30 (m, 1H), 1.19 (s, 3H), 0.93 (s, 6H).

## Example 340

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[2-(cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 340A

4-(1,4-dioxaspiro[4.5]decan-8-ylamino)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-3-nitrobenzenesulfonamide (1.4 g) in tetrahydrofuran (30 mL) was added 1,4-dioxaspiro[4.5]decan-8-amine (1.0 g) and diisopropylethylamine (5 mL). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 340B

N-(4-(1,4-dioxaspiro[4.5]decan-8-ylamino)-3-nitrophenylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

To a solution of EXAMPLE 3J (617 mg) and EXAMPLE 340A (386 mg) in dichloromethane (10 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (288 mg) and 4-(dimethylamino)pyridine (183 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous

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NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 340C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(4-oxocyclohexylamino)phenylsulfonyl)benzamide

To a solution of EXAMPLE 340B (386 mg) in acetone (10 mL) and water (5 mL) was added para-toluenesulfonic acid monohydrate (50 mg). The mixture was stirred at 120° C. in a Biotage Initiator microwave reactor for 30 minutes. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 340D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((2-cyanoethyl)(cyclopropyl)amino)cyclohexyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 340C (240 mg) and 3-(cyclopropylamino)propanenitrile (62 mg) in tetrahydrofuran (10 mL) was added acetic acid (2 mL) and MP-cyanoborohydride (300 mg, 2.15 mmol/g). The mixture was stirred overnight. The mixture was filtered and concentrated under vacuum and the residue was dissolved in dimethylsulfoxide/methanol (1:1, 10 mL) and loaded on Gilson, C18(100A) 250×121.2 mm (10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.55 (dd, 1H), 8.17 (d, 1H), 8.03 (d, 1H), 7.79 (d, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.11 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (d, 1H), 6.19 (d, 1H), 4.01 (m, 1H), 3.56 (m, 1H), 3.06 (m, 4H), 2.88 (t, 2H), 2.65 (m, 6H), 2.19 (m, 6H), 2.00 (m, 7H), 1.51 (m, 6H), 0.92 (s, 6H), 0.42 (m, 4H).

## Example 341

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-({5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl}methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 341A

ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (31.8 g) in toluene (100 mL) was added ethylene glycol (36.5 mL) and p-toluenesulfonic acid monohydrate (0.426 g). The two phase mixture was stirred rapidly at ambient temperature for 72 hours. The reaction was diluted with water (900 mL) and extracted with ether (900 mL). The organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulfate. After filtration, the title compound was obtained by concentration under high vacuum.

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Example 341B

1,4-dioxaspiro[4.5]decane-8-ylmethanol

To a suspension of lithium aluminum hydride (8.19 g) in tetrahydrofuran (400 mL) was added dropwise a solution of EXAMPLE 341A (37.8 g) in tetrahydrofuran (75 mL). The mixture was then heated at reflux for 2 hours. The reaction mixture was cooled in an ice bath and quenched very slowly with water (8 mL). Then added sequentially were 4N sodium hydroxide (8 mL), ether (200 mL), water (24 mL), ether (500 mL) and anhydrous sodium sulfate (250 g). The resulting mixture was stirred rapidly for 2 hours and was filtered. The title compound was isolated by concentration of the filtrate.

## Example 341C

8-(benzyloxymethyl)-1,4-dioxaspiro[4.5]decane

To a suspension of sodium hydride (60% oil dispersion, 8.86 g) in tetrahydrofuran (170 mL) was added a solution of EXAMPLE 341B (30.52 g) in tetrahydrofuran (100 mL). This mixture was stirred for 30 minutes and benzyl bromide (24 mL) was added. After stirring for 72 hours, the reaction was quenched with saturated ammonium chloride solution (400 mL) and diluted with ether (500 mL). The layers were separated and the aqueous layer was extracted with ether (2×150 mL). The combined organics were dried over sodium sulfate, filtered and concentrated. The crude product was purified on silica gel eluting with a 0, 10, 15, 75% ethyl acetate in hexanes step gradient to provide the title compound.

## Example 341D

4-(benzyloxymethyl)cyclohexanone

To a solution of EXAMPLE 341C (43.02 g) in dioxane (500 mL) was added water (125 mL) and 2M hydrochloric acid (90 mL). The mixture was heated at 85° C. for 18 hours. Upon cooling, the reaction mixture was diluted with brine (1500 mL), saturated sodium bicarbonate solution (300 mL) and ether (1000 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified on silica gel eluting with a 5-50% ethyl acetate in hexanes step gradient to provide the title compound.

## Example 341E

trans-4-(benzyloxymethyl)-1-methylcyclohexanol

To 2,6-di-*t*-butyl-4-methylphenol (83.4 g) in toluene (1100 mL) was added 2.0M (in hexanes) trimethylaluminum (95 mL) somewhat carefully to control methane evolution and a small exotherm. The reaction mixture was stirred at ambient temperature under N<sub>2</sub> for 75 minutes and was then cooled to -77° C. A solution of EXAMPLE 341D (14 g) in toluene (15 mL) was added dropwise, keeping the temperature below -74° C. Methyl lithium (1.6M in diethyl ether, 120 mL) was then added dropwise, keeping the temperature below -65° C. The resulting mixture was stirred at -77° C. under N<sub>2</sub> for 2 hours. The reaction mixture was then poured into 1N aqueous HCl (1600 mL), rinsing the flask with toluene. The organic layer was washed with brine and the combined aqueous layers were extracted with diethyl ether. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on 650 g of spherical silica gel



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using 2.5 L of 80/20 hexanes/ethyl acetate, then 3.0 L of 75/25 hexanes/ethyl acetate, and finally 4.0 L of 70/30 hexanes/ethyl acetate as the eluents to provide the title compound.

## Example 341F

Trans-4-(hydroxymethyl)-1-methylcyclohexanol

EXAMPLE 341E (12.6 g) and ethanol (120 ml) were added to 20% Pd(OH)<sub>2</sub>/C, wet (1.260 g) in a 500 mL SS pressure bottle. The reaction mixture was stirred at ambient temperature under 30 psi hydrogen gas. Hydrogen uptake ceased at 5 minutes. The mixture was filtered through a nylon membrane rinsing with ethanol. The filtrate was concentrated and then azeotroped with toluene (100 mL) to remove any remaining ethanol. The concentrate was dried under high vacuum for 40 minutes to provide the title compound.

## Example 341G

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 341F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 341H

N-({5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-yl}sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J and EXAMPLE 341G for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.09 (s, 1H), 9.18 (d, 1H), 8.74 (d, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.67 (m, 2H), 7.42 (m, 2H), 7.09 (m, 2H), 6.74 (dd, 1H), 6.52 (dd, 1H), 6.49 (d, 1H), 4.29 (d, 2H), 3.05 (m, 4H), 2.80 (s, 2H), 2.37 (t, 2H), 2.15 (m, 4H), 2.11 (s, 2H), 1.89 (m, 6H), 1.75 (m, 2H), 1.45 (t, 2H), 1.41 (s, 3H), 1.32 (m, 2H), 0.37 (m, 4H).

## Example 342

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 342A

methyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylate

To a 50 ml pressure bottle were placed methyl imidazo[1,2-a]pyridine-6-carboxylate (0.26 g), acetic acid (10 ml), and wet 5% palladium on carbon (0.052 g). The reaction mixture was stirred for 16 hours at 30 psi and 50° C. The solid was filtered off, and the filtrate was concentrated. The residue was taken up in ethyl acetate. It was then washed with saturated sodium bicarbonate, brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chro-

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matography on silica gel using 10-100% ethyl acetate in hexanes to provide the title compound.

## Example 342B

(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methanol

The title compound was prepared by substituting EXAMPLE 342A for EXAMPLE 339A in EXAMPLE 339B.

## Example 342C

5-chloro-6-((5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 342B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

## Example 342D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 342C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.54 (s, 1H), 8.36 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.58 (d, 1H), 7.41-7.44 (m, 2H), 7.2-7.36 (m, 4H), 7.05 (d, 2H), 6.63 (dd, 1H), 6.32 (dd, 1H), 6.24 (d, 1H), 4.42-4.51 (m, 1H), 4.37-4.40 (m, 1H), 4.29 (dd, 1H), 3.91 (dd, 1H), 3.03 (s, 4H), 2.90-2.95 (m, 2H), 2.77 (s, 2H), 2.51-2.52 (m, 1H), 2.07-2.23 (m, 7H), 1.96 (s, 2H), 1.76-1.82 (m, 1H), 1.65-1.69 (m, 2H), 1.54-1.56 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 343

N-[(5-chloro-6-((1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl)methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 343A

5-chloro-6-(((1S,2S,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was isolated as another isomer in EXAMPLE 339C.

## Example 343B

5-chloro-6-(((1S,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 343A for EXAMPLE 339B in EXAMPLE 339C.

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## Example 343C

N-[(5-chloro-6-[[1R,2S,4R,5R]-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 343B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.49-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.27 (s, 1H), 4.11-4.19 (m, 2H), 3.11 (s, 4H), 2.87 (s, 2H), 1.96-2.23 (m, 10H), 1.88 (d, 1H), 1.50 (dd, 1H), 1.33-1.44 (m, 2H), 1.13-1.19 (m, 4H), 0.88-0.93 (m, 8H).

## Example 344

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 344A

4-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

EXAMPLE 347A (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.2 g) in tetrahydrofuran (40 mL) were treated with 60% sodium hydride (1.6 g) for 3 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by a reverse phase chromatography, eluting with 30-50% CH<sub>3</sub>CN in 0.1% trifluoroacetic acid water to provide the title compound as a single enantiomer.

## Example 344B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 344A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.34 (d, 1H), 8.04 (m, 2H), 7.52 (m, 3H), 7.40 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.96 (s, 1H), 3.10 (br s, 4H), 2.85 (m, 2H), 2.29 (m, 3H), 2.15 (t, 2H), 1.96 (br s, 2H), 1.68 (m, 1H), 1.55 (m, 4H), 1.42 (m, 4H), 1.27 (m, 2H), 1.10 (s, 3H), 0.92 (s, 6H).

## Example 345

N-[(5-chloro-6-[[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J and EXAMPLE 277O

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for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.13 (d, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.68 (t, 1H), 7.66 (d, 1H), 7.42 (m, 2H), 7.09 (m, 2H), 6.75 (dd, 1H), 6.51 (m, 2H), 4.64 (d, 4H), 4.53 (d, 2H), 3.39 (m, 1H), 3.06 (m, 4H), 2.81 (s, 2H), 2.51 (m, 2H), 2.37 (m, 2H), 2.12 (m, 10H), 1.90 (m, 2H), 1.45 (t, 2H), 0.38 (s, 4H).

## Example 346

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[3,3-difluoropyrrolidin-1-yl]cyclohexyl}amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 3,3-difluoropyrrolidine hydrochloride for 3-(cyclopropylamino)propanenitrile in EXAMPLE 340D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.38 (m, 1H), 8.55 (m, 1H), 8.36 (d, 1H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.13 (d, 1H), 7.04 (d, 2H), 6.83 (m, 1H), 6.68 (m, 1H), 6.38 (d, 1H), 6.19 (s, 1H), 4.02 (s, 1H), 3.83 (m, 1H), 3.06 (m, 4H), 2.96 (m, 2H), 2.73 (m, 4H), 2.26 (m, 8H), 1.97 (m, 4H), 1.68 (m, 4H), 1.37 (m, 2H), 0.92 (s, 6H).

## Example 347

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 347A

4-(hydroxymethyl)-1-methylcyclohexanol

4-(Hydroxymethyl)cyclohexanone (800 mg) in tetrahydrofuran (15 mL) was treated with 3 M methylmagnesium chloride in tetrahydrofuran (6.24 mL) at 0° C. The reaction was warmed to room temperature over 2 hours and quenched with methanol and water. The resulting mixture was concentrated and the residue was suspended in ethyl acetate. The precipitates were filtered off and the filtrate was concentrated. The residue was purified by chromatography, eluting with 0-100% ethyl acetate in hexane to provide the title compound.

## Example 347B

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

EXAMPLE 347A (970 mg) and EXAMPLE 40A (1.6 g) in N,N-dimethylformamide (8 mL) were treated with sodium hydride (1.8 g, 60%) at room temperature for 2 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by a reverse phase chromatography, eluting with 30-45% acetonitrile in 0.1% trifluoroacetic acid water to isolate the title compound.

## Example 347C

5-chloro-6-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared and isolated as described in Example 347B.

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## Example 347D

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 347B in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.51 (d, 1H), 8.18 (d, 1H), 8.03 (d, 1H), 7.48-7.56 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.17-4.34 (m, 3H), 3.11 (s, 4H), 2.89 (s, 2H), 2.24-2.42 (m, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.66-1.82 (m, 3H), 1.55 (d, 2H), 1.31-1.44 (m, 4H), 1.12-1.27 (m, 2H), 1.10 (s, 3H), 0.93 (s, 6H).

## Example 348

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 347C in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.51 (d, 1H), 8.18 (d, 1H), 8.03 (d, 1H), 7.47-7.58 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.21 (d, 2H), 3.95 (s, 1H), 3.11 (s, 4H), 2.89 (s, 2H), 2.33 (d, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.77 (m, 1H), 1.48-1.60 (m, 4H), 1.35-1.48 (m, 4H), 1.20-1.33 (m, 2H), 1.09 (s, 3H), 0.93 (s, 6H).

## Example 349

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[2,2-difluorocyclopropyl]amino}cyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 2,2-difluorocyclopropanamine hydrochloride for 3-(cyclopropylamino)propanenitrile in EXAMPLE 340D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.47 (m, 2H), 8.12 (m, 1H), 7.98 (m, 1H), 7.72 (m, 2H), 7.47 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.65 (dd, 1H), 6.35 (m, 1H), 6.22 (d, 1H), 3.54 (m, 2H), 3.08 (m, 4H), 2.74 (m, 4H), 2.25 (m, 4H), 2.01 (m, 4H), 1.38 (m, 4H), 0.92 (s, 6H).

## Example 350

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 350A

ethyl spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-carboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (22.75 g) and pyrocatechol (14.75 g) in toluene (200 mL) was added

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catalytic amount of para-toluenesulfonic acid monohydrate and the mixture was stirred under reflux and a Dean-Stark trap overnight. The mixture was diluted with diethyl ether (600 mL) and washed with aqueous NaHCO<sub>3</sub>, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

## Example 350B

ethyl 4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-carboxylate

A solution of EXAMPLE 350A (5.25 g) in tetrahydrofuran (40 mL) was added dropwise to a solution of lithium diisopropylamide (12 mL, 2.0M in tetrahydrofuran/heptane/ethylbenzene) at 0° C. The solution was stirred at 0° C. for 30 minutes, and then was transferred by cannula to a pre-cooled (0° C.) stirring solution of N-fluorobenzenesulformimide (7.89 g) in dry tetrahydrofuran (20 mL). The reaction mixture was stirred at 0° C. for 30 minutes, and then at 20° C. for 18 hours. The reaction mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with diethyl ether (3×200 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the crude product.

## Example 350C

(4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methanol

To a solution of EXAMPLE 350B (23 g) in tetrahydrofuran (150 mL) was added lithium aluminum hydride (3.11 g). The mixture was stirred overnight. Aqueous 2N NaOH solution was added dropwise to the reaction mixture. The mixture was then diluted with ethyl acetate (600 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the crude product which was loaded on a 600 g analogics column and eluted with 10% to 20% ethyl acetate in hexane to provide the title compound.

## Example 350D

5-chloro-6-((4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350C (89 mg) in N,N-dimethylformamide (3 mL) was added NaH (65% in mineral oil, 36 mg). The mixture was stirred for 30 minutes, and then 5,6-dichloropyridine-3-sulfonamide (85 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate (100 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, the residue was loaded on a silica gel cartridge and eluted with 30% ethyl acetate in hexane to provide the title compound.

## Example 350E

5-chloro-6-((1-fluoro-4-oxocyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350D (1.6 g) and pyridinium p-toluenesulfonate (1.2 g) in acetone (10 mL) was added

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water (2 mL) and the mixture was stirred under microwave irradiation at 100° C. for 10 minutes. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 350F

## 5-chloro-6-((cis-1-fluoro-4-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350E (336 mg) in tetrahydrofuran (10 mL) was added NaBH<sub>4</sub> (75 mg). The mixture was stirred for 45 minutes. The mixture was diluted with ethyl acetate (300 mL) and washed with 2N aqueous NaOH, water, and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated to give the crude product.

## Example 350G

## N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 350F for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.48 (s, 1H), 8.18 (s, 1H), 8.01 (d, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.62 (d, 1H), 4.47 (s, 1H), 4.40 (s, 1H), 3.46 (m, 1H), 3.06 (m, 4H), 2.88 (m, 1H), 2.25 (m, 6H), 1.99 (m, 4H), 1.58 (m, 8H), 0.93 (s, 6H).

## Example 351

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 351A

## diethyl 1,4-dioxaspiro[4.5]decane-8,8-dicarboxylate

A 500 mL round-bottomed flask was charged with diisopropylamine (16 mL) and tetrahydrofuran (311 mL). The solution was cooled to -78° C. under N<sub>2</sub> and n-BuLi (2.5 M in hexanes, 44.8 mL) was added. The reaction was stirred for 30 minutes at -78° C. and ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (20 g) was added as a tetrahydrofuran solution (ca. 10 mL). The solution was stirred at -78° C. for 1 hour and ethyl chloroformate (9 mL) was added neat. After stirring at -78° C. for 10 minutes, the reaction was warmed to room temperature over 2 hours. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and was diluted with diethyl ether. The layers were separated, the aqueous layer was extracted with diethyl ether and the combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes/ethyl acetate).

## Example 351B

## 1,4-dioxaspiro[4.5]decane-8,8-diyl dimethanol

To a 1 L round-bottomed flask was added EXAMPLE 351A (26.6 g) and tetrahydrofuran (310 mL) to give a color-

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less solution. The solution was cooled to 0° C. and lithium aluminum hydride (2M in tetrahydrofuran, 62 mL) was added via syringe. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was cooled back down to 0° C. and quenched slowly with 4.7 mL water, 4.7 mL 10% aqueous NaOH and 14 mL water. The mixture was allowed to stir until salts were formed and was then filtered through a Supelco 90 mm silica gel Buchner funnel. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-80% hexanes/ethyl acetate).

## Example 351C

## 2,8,11-trioxa-dispiro[3.2.4]tridecane

To a 1 L round-bottomed flask was added EXAMPLE 351B (13 g) in tetrahydrofuran (321 mL). The solution was cooled to -78° C. under N<sub>2</sub> and n-BuLi (25.7 mL) was added dropwise via syringe. After addition was complete, the mixture stirred for 30 minutes and a tetrahydrofuran solution of 4-toluenesulfonyl chloride (12.25 g) was added via addition funnel. The reaction was allowed to stir overnight, and gradually warm to room temperature. The reaction mixture was cooled to -78° C. and n-BuLi (25.7 mL) was added. The mixture was warmed to room temperature and stirred for 3 hours. The reaction was quenched with sat aqueous NH<sub>4</sub>Cl and diluted with diethyl ether. The layers were separated, the aqueous layers extracted with diethyl ether and the combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-20% acetone/hexanes).

## Example 351D

## 2-oxaspiro[3.5]nonan-7-one

To a 500 mL round-bottomed flask was added EXAMPLE 351C (11 g) in 80% aqueous acetic acid (200 mL). The reaction was heated to 65° C. and stirred for about 4 hours. Most of the acetic acid and water were removed by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes/ethyl acetate).

## Example 351E

## 7-methylene-2-oxaspiro[3.5]nonane

To a 250 mL round-bottomed flask was added methyltriphenylphosphonium iodide (4.33 g) in tetrahydrofuran (35.7 mL) to give a suspension. The suspension was cooled to -15° C. n-BuLi (2.5 M in hexanes, 4.28 mL) was added dropwise and the mixture was stirred at -15° C. for 40 minutes and EXAMPLE 351D (1 g) was added as a tetrahydrofuran (ca. 5 mL) solution. The mixture was stirred at -15° C. for about 15 minutes and warmed to room temperature. After 1.5 hours, the reaction was complete and was quenched with saturated aqueous NH<sub>4</sub>Cl and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted (2×) with diethyl ether. The combined organics were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase chromatography (Analogix, 80 g Grace silica gel column, 0-50% hexanes/ethyl acetate).



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Example 351F

## 2-oxaspiro[3.5]nonan-7-ylmethanol

To a 25 mL round-bottomed flask was added EXAMPLE 351E (568 mg) and EXAMPLE 351F tetrahydrofuran (4.11 mL) to give a colorless solution. 9-Borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran, 24.7 mL) was added and the reaction was allowed to stir for 2 hours at room temperature. Ethanol (11 mL) was added followed by aqueous NaOH (5M, 4.11 mL) and then hydrogen peroxide (2.1 mL) was added. The reaction was heated at 50° C. for 2 hours. The mixture was concentrated by rotary evaporation, and diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3×) and the combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 80 g Grace, 0-70% hexanes/ethyl acetate).

## Example 351G

## 4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-3-nitrobenzenesulfonamide

EXAMPLE 351G was prepared substituting EXAMPLE 351F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 351H

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 351G for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H) 8.34 (s, 1H) 8.03 (d, 2H) 7.45-7.57 (m, 3H) 7.30-7.40 (m, 3H) 7.04 (d, 2H) 6.67 (dd, 1H) 6.39 (dd, 1H) 6.17-6.23 (m, 1H) 4.29 (s, 2H) 4.20 (s, 2H) 4.00 (d, 2H) 3.08 (s, 4H) 2.73-2.90 (m, 2H) 2.72 (s, 1H) 2.01-2.32 (m, 6H) 1.96 (s, 2H) 1.64-1.78 (m, 4H) 1.33-1.50 (m, 6H) 0.96-1.15 (m, 2H) 0.92 (s, 6H).

## Example 352

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 352A

## 4-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 341F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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Example 352B

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 352A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.31 (br s, 1H), 8.01 (m, 2H), 7.49 (m, 3H), 7.33 (m, 3H), 7.03 (m, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.19 (d, 1H), 4.27 (s, 1H), 4.05 (d, 2H), 3.40 (m, 2H), 3.17 (s, 1H), 3.07 (m, 3H), 2.79 (m, 1H), 2.24 (m, 3H), 2.14 (m, 2H), 1.94 (m, 2H), 1.71 (m, 3H), 1.52 (m, 2H), 1.38 (m, 4H), 1.22 (m, 2H), 1.09 (s, 3H), 0.91 (s, 6H).

## Example 353

## 4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 353A

## 1,4-dioxaspiro[4.5]decane-8,8-diylbis(methylene)bis(4-methylbenzenesulfonate)

To a 500 mL round-bottomed flask was added EXAMPLE 351B (10 g) and dichloromethane (165 mL) to give a colorless solution. Triethylamine (24.1 mL) and toluene-2-sulfonyl chloride (19.8 g) were added followed by 4-dimethylaminopyridine (0.604 g). The reaction was refluxed overnight. Saturated aqueous NH<sub>4</sub>Cl was added followed by dilution with water and additional dichloromethane. The aqueous layer was extracted with dichloromethane (2×) and the combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-55% hexanes/ethyl acetate).

## Example 353B

## 8,8-bis(fluoromethyl)-1,4-dioxaspiro[4.5]decane

To a 500 mL round-bottomed flask was added EXAMPLE 353A (20 g). tetra-n-Butylammonium fluoride (1M in tetrahydrofuran, 200 mL) was added and the resulting solution was refluxed for 6 days. The reaction was cooled, diluted with diethyl ether and washed with water (3×). The organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-30% hexanes/ethyl acetate).

## Example 353C

## 4,4-bis(fluoromethyl)cyclohexanone

To a 250 mL round bottom flask was added EXAMPLE 353B (1.1 g) and 80% aqueous acetic acid (50 mL). The reaction was heated at 65° C. for 3 hours, cooled and concentrated by rotary evaporation to remove most of the acetic acid

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and water. The residue was purified by regular phase flash column chromatography (Analogix, 0-50% hexanes/ethyl acetate).

## Example 353D

## 2-chloro-5,5-bis(fluoromethyl)cyclohex-1-enecarbaldehyde

To a 100 mL pear flask was added N,N-dimethylformamide (498  $\mu$ A) and dichloromethane (8.9 mL) to give a colorless solution. The solution was cooled to 0° C. and POCl<sub>3</sub> (550  $\mu$ A) was added dropwise and then the mixture was warmed to room temperature for 30 minutes. In the meantime, to a 100 mL pear shaped flask was added EXAMPLE 353C (870 mg, 5.36 mmol) in dichloromethane (8941  $\mu$ l) to give a colorless solution. The Vilsmeier reagent was then taken up in a syringe and added dropwise to the 4,4-bis(fluoromethyl)cyclohexanone (870 mg) solution at room temperature. The resulting solution was stirred overnight. The reaction was poured into saturated aqueous NaHCO<sub>3</sub> and ice, warmed to room temperature and extracted with dichloromethane (3 $\times$ 30 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix (0-60% hexanes/ethyl acetate).

## Example 353E

## 2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enecarbaldehyde

To a 20 mL vial was added EXAMPLE 353D (460 mg), 4-chlorophenylboronic acid (414 mg), potassium carbonate (762 mg), tetrabutylammonium bromide (711 mg), palladium (II) acetate (14.85 mg) and water (2450  $\mu$ A) to give a suspension which was degassed with N<sub>2</sub> for 2 minutes. The reaction was stirred at 45° C. overnight, cooled, and poured over a Supelco silica gel Buchner funnel, washing with ethyl acetate several times. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-60% hexanes/ethyl acetate).

## Example 353F

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

To a 20 mL vial was added EXAMPLE 353E (240 mg), EXAMPLE 15F (297 mg) and dichloromethane (4.2 mL). Sodium triacetoxyborohydride (268 mg) was added and the reaction was stirred overnight at room temperature. The reaction was loaded directly onto silica gel and purified by regular phase flash column chromatography (Analogix, 0-80% hexanes/ethyl acetate).

## Example 353G

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 353F for EXAMPLE 15G in EXAMPLE 15H.

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## Example 353H

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

EXAMPLE 353H was prepared by replacing EXAMPLE 3J with EXAMPLE 353G and EXAMPLE 11B with EXAMPLE 1F in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>)  $\delta$  11.69 (s, 1H) 11.44 (s, 1H) 8.48-8.70 (m, 1H) 8.05 (d, 2H) 7.81 (dd, 1H) 7.46-7.59 (m, 3H) 7.35 (d, 2H) 7.12 (d, 2H) 6.68 (dd, 1H) 6.40 (dd, 1H) 6.16 (d, 1H) 4.39-4.49 (m, 2H) 4.23-4.35 (m, 2H) 3.85 (dd, J=11.87, 2.71 Hz, 2H) 3.20-3.30 (m, 4H) 2.98-3.10 (m, 4H) 2.66-2.77 (m, 2H) 2.11-2.30 (m, 6H) 2.02-2.12 (m, 3H) 1.99 (s, 1H) 1.82-1.97 (m, 1H) 1.54-1.67 (m, 4H) 1.20-1.34 (m, 2H).

## Example 354

## 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-(4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 354A

## tert-butyl 2-((2-nitro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol EXAMPLE 24A.

## Example 354B

## 4-(morpholin-2-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 354A for EXAMPLE 113A in EXAMPLE 134A.

## Example 354C

## 4-((4-cyclopropylmorpholin-2-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 354B for EXAMPLE 173A in EXAMPLE 173B.

## Example 354D

## 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-(4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 354C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>)  $\delta$  12.98 (s, 1H), 9.06 (d, 1H), 8.50 (dd, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.66 (t, 1H), 7.62 (d, 1H), 7.44 (d, 2H), 7.26 (d, 1H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.31 (dd, 1H), 4.22 (dd, 1H),

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3.92 (m, 1H), 3.83 (d, 1H), 3.56 (dt, 1H), 3.07 (m, 5H), 2.77 (s, 2H), 2.68 (d, 1H), 2.35 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.59 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.40 (m, 4H).

Example 355

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 355A

5-chloro-6-((trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

To a cooled (0° C.) solution of EXAMPLE 350E (1.2 g) in tetrahydrofuran (30 mL) was added dropwise a solution of methylmagnesium bromide (5 mL, 3.0M in ether). Upon addition, the reaction mixture solidified. More tetrahydrofuran (10 mL) was added to the mixture and stirring was continued for 1 hour. The mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The mixture was filtered and concentrated. The residue was dissolved in dimethylsulfoxide/methanol (20 mL, 1:1) and loaded on Gilson, C18(100A) 250×121.2 mm (10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes to separate the two isomers and isolate the title compound.

Example 355B

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 355A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 7.54 (d, 1H), 7.48 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.22 (d, 1H), 4.49 (s, 1H), 4.42 (s, 1H), 4.15 (s, 1H), 3.06 (m, 4H), 2.84 (m, 1H), 2.25 (m, 6H), 1.96 (s, 3H), 1.83 (m, 4H), 1.44 (m, 6H), 1.14 (s, 3H), 0.93 (s, 6H).

Example 356

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 356A

5-chloro-6-((cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 355A.

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Example 356B

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 356A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.52 (s, 1H), 8.20 (s, 1H), 8.03 (d, 1H), 7.51 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.55 (s, 1H), 4.48 (s, 1H), 4.34 (s, 1H), 3.08 (m, 4H), 2.89 (d, 2H), 2.27 (m, 5H), 1.93 (m, 4H), 1.66 (m, 4H), 1.43 (m, 4H), 1.11 (s, 3H), 0.93 (s, 6H).

Example 357

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 357A

ethyl

4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

To 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.000 g) was added HCl (4.0M in dioxane, 4.54 mL). After 1 hour the reaction was concentrated and dried under high vacuum. The resulting solid was dissolved in dichloromethane (5 mL) and treated with sodium triacetoxyborohydride (1.155 g) and oxetan-3-one (0.262 g) and stirred overnight. The reaction was quenched with saturated NaHCO<sub>3</sub> solution (20 mL) and extracted into dichloromethane (2×25 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting with a gradient of 0.5% to 3.75% methanol/dichloromethane over 40 minutes (flow=30 mL/min) gave the title compound.

Example 357B

(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

To a solution of EXAMPLE 357A (0.59 g) in tetrahydrofuran (5 mL) was added lithium aluminum hydride (1.80 mL) at 0° C. The reaction was removed from the ice bath and allowed to warm to room temperature. The reaction was quenched by the dropwise addition of 0.6 mL of water followed by 0.2 mL of 2N aqueous NaOH. The reaction was filtered through celite and rinsed with ethyl acetate (50 mL). The mixture and the residue was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minutes (flow=40 mL/minutes) to provide the title compound.

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## Example 357C

3-cyano-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 357B for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 284A.

## Example 357D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 357C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.49-11.14 (m, 1H), 8.17 (d, 1H), 8.03 (d, 2H), 7.51 (dd, 3H), 7.43-7.26 (m, 3H), 7.12-6.96 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.55 (t, 2H), 4.45 (t, 2H), 4.34 (d, 2H), 3.49 (s, 1H), 3.09 (s, 8H), 2.39-1.66 (m, 14H), 1.39 (s, 2H), 0.92 (s, 6H).

## Example 358

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 358A

## benzyl

(4-ethyl-4-hydroxycyclohexyl)methylcarbamate

To a vigorous stirring solution of benzyl (4-oxocyclohexyl)methylcarbamate (1 g) in tetrahydrofuran (20 mL) at -78° C. was slowly added 1 M ethylmagnesium bromide (11.48 mL, 11.48 mmol) in ether. After completion of the addition, the mixture was stirred at -78° C. for 2 hours and was warmed to 0° C., and stirred in an ice bath for 30 minutes. The reaction was quenched with a cold NH<sub>4</sub>Cl aqueous solution. The precipitates were filtered off and washed with ethyl acetate. The filtrate was concentrated. The residue was dissolved in dichloromethane and loaded onto Analogix purification system, and was eluted with 0-50% ethyl acetate in dichloromethane to provide the title compound.

## Example 358B

4-(aminomethyl)-1-ethylcyclohexanol

A mixture of EXAMPLE 358A (500 mg) and 10% Pd/C (100 mg) in tetrahydrofuran (15 mL) was stirred under H<sub>2</sub> for 3 hours. The insoluble material was removed by filtration, and the filtrate was concentrated to provide the title compound.

## Example 358C

4-((trans-4-ethyl-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 358B (270 mg) and 4-fluoro-3-nitrobenzenesulfonamide (417 mg) in tetrahydrofuran were treated with

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triethylamine (0.8 mL) overnight. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by a reverse phase chromatography, eluting with 40-55% acetonitrile in 0.1% trifluoroacetic acid water to isolate the title compound.

## Example 358D

4-((cis-4-ethyl-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared and isolated as described in Example 358C.

## Example 358E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 358C in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.35 (s, 1H), 8.56 (d, 2H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.45-7.57 (m, 3H), 7.34 (d, 2H), 7.00-7.10 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.98 (s, 1H), 3.24-3.31 (m, 4H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.54-1.73 (m, 5H), 1.35-1.47 (m, 4H), 1.20-1.32 (m, 2H), 1.03-1.18 (m, 2H), 0.92 (s, 6H), 0.81 (t, 3H).

## Example 359

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 358D in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.34 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.54 (d, 1H), 7.47-7.52 (m, 2H), 7.34 (d, 2H), 7.01-7.10 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.77 (s, 1H), 3.26 (t, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.10-2.26 (m, 6H), 1.95 (s, 2H), 1.46-1.61 (m, 5H), 1.28-1.46 (m, 6H), 1.12-1.24 (m, 2H), 0.92 (s, 6H), 0.82 (t, 3H).

## Example 360

4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 360A

## ethyl

8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

Into a 500 mL round-bottomed flask was added diisopropylamine (7.98 mL) in tetrahydrofuran (233 mL) to give a



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colorless solution. The mixture was cooled to  $-78^{\circ}\text{C}$ . under  $\text{N}_2$  and n-BuLi (2.5 M in hexanes, 22.40 mL) was added. The reaction was stirred for 30 minutes and ethyl 1,4-dioxaspiro [4.5]decane-8-carboxylate (10 g) was added. The reaction was allowed to stir for 1.5 hours upon which time  $\text{CH}_3\text{I}$  (4.38 mL) was added. The reaction was allowed to warm to room temperature overnight with stirring. Water was added and the aqueous layer was extracted with ethyl acetate. The combined organics were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated by rotary evaporation. The residue was purified by normal phase flash column chromatography (Analogix, 0-50% hexanes/ethyl acetate).

## Example 360B

(8-methyl-1,4-dioxaspiro[4.5]decane-8-yl)methanol

In a 500 mL, round-bottomed flask was lithium aluminum hydride (1.772 g) in tetrahydrofuran (234 mL) to give a suspension. This suspension was cooled to  $0^{\circ}\text{C}$ . and ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (10.66 g) was added via addition funnel. The reaction was stirred overnight at room temperature and then cooled back down to  $0^{\circ}\text{C}$ . The excess lithium aluminum hydride was slowly quenched with 1.8 mL water, 1.8 mL aqueous NaOH (5N) and 5.6 mL water. The suspension was stirred until the salts turned white and was then filtered through a plug of silica gel. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-75% hexanes/ethyl acetate).

## Example 360C

8-(methoxymethyl)-8-methyl-1,4-dioxaspiro[4.5]decane

To a 250 mL round-bottomed flask was added NaH (0.902 g) and tetrahydrofuran (37.6 mL) to give a suspension. EXAMPLE 360B was added as a tetrahydrofuran solution at room temperature. The suspension was stirred for 30 minutes and then  $\text{CH}_3\text{I}$  (0.611 mL) was added. The reaction was stirred under  $\text{N}_2$  overnight, carefully quenched with brine and diluted with water and ether. The aqueous layer was extracted with ether (2x) and the combined organics were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography (Analogix, 0-60% hexanes/ethyl acetate).

## Example 360D

4-(methoxymethyl)-4-methylcyclohexanone

The title compound was prepared by substituting EXAMPLE 360C for EXAMPLE 353B in EXAMPLE 353C.

## Example 360E

2-chloro-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 360D for EXAMPLE 353C in EXAMPLE 353D.

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## Example 360F

2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 360E for EXAMPLE 353D in EXAMPLE 353E.

## Example 360G

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 360F for EXAMPLE 353E in EXAMPLE 353F.

## Example 360H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 360G for EXAMPLE 15G in EXAMPLE 15H.

## Example 360I

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

The title compound was prepared by replacing EXAMPLE 3J with EXAMPLE 360H and EXAMPLE 11B with EXAMPLE 1F in EXAMPLE 11D.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.68 (s, 1H) 11.43 (s, 1H) 8.45-8.72 (m, 2H) 8.04 (d, 1H) 7.80 (dd, 1H) 7.44-7.61 (m, 3H) 7.34 (d, 2H) 6.99-7.20 (m, 3H) 6.68 (dd, 1H) 6.39 (dd, 1H) 6.18 (d, 1H) 3.85 (dd, 2H) 3.25-3.30 (m, 4H) 3.24 (s, 3H) 3.02-3.17 (m, 6H) 2.72 (dd, 2H) 2.18 (s, 5H) 2.03-2.13 (m, 2H) 1.81-1.93 (m, 2H) 1.57-1.67 (m, 2H) 1.47-1.56 (m, 1H) 1.17-1.41 (m, 3H) 0.91 (s, 3H).

## Example 361

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((2S)-4-(oxetan-3-yl)morpholin-2-yl)methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 361A

(S)-3-nitro-4-((4-(oxetan-3-yl)morpholin-2-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259E for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

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Example 361B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-  
([(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl)amino]phenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 361A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.96 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.64 (m, 4H), 3.93 (m, 1H), 3.89 (d, 1H), 3.68 (dt, 1H), 3.53-3.35 (m, 3H), 3.07 (m, 4H), 2.77 (s, 2H), 2.72 (d, 1H), 2.44 (d, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.85 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

Example 362

N-(3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 362A

3-chloro-4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 341F (300 mg) in N,N-dimethylformamide (10 mL) was added sodium hydride (416 mg) portionwise. The resulting suspension was stirred for 15 minutes. 3-Chloro-4-fluorobenzenesulfonamide (425 mg) was added and stirring was continued for 72 hours. The reaction was quenched with water and the pH was adjusted to ca. 7. The mixture was diluted with brine (75 mL) and extracted with methylene chloride. The crude product was isolated from the dried methylene chloride layer by concentration and was purified on silica gel eluted with a 10, 25, 50% ethyl acetate in methylene chloride step gradient to provide the title compound.

Example 362B

N-(3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 362A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.07 (m, 1H), 8.58 (d, 1H), 8.45 (d, 1H), 8.31 (dd, 1H), 8.11 (d, 1H), 7.69-7.67 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.97 (d, 1H), 6.74 (dd, 1H), 6.52 (m, 2H), 5.34 (br s, 2H), 3.82 (d, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97-1.85 (m, 7H), 1.82-1.73 (m, 2H), 1.44-1.32 (m, 7H), 0.94 (m, 6H).

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Example 363

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[2-(cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 363A

4-((4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 350C (495 mg) in N,N-dimethylformamide (6 mL) was added NaH (65% in mineral oil, 320 mg). The mixture was stirred for 30 minutes, and then 4-fluoro-3-nitrobenzenesulfonamide (457 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate (300 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, the residue was loaded on a silica gel cartridge and was eluted with 30% ethyl acetate in hexane to provide the title compound.

Example 363B

4-((1-fluoro-4-oxocyclohexyl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 363A (860 mg) in ethanol (30 mL) was added concentrated HCl (10 mL) and the mixture was stirred at 100° C. for 3 hours. The mixture was neutralized with solid Na<sub>2</sub>CO<sub>3</sub> and extracted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

Example 363C

4-((4-((2-cyanoethyl)(cyclopropyl)amino)-1-fluorocyclohexyl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 363B (200 mg) in dichloromethane (6 mL) was added 3-(cyclopropylamino)propanenitrile (64 mg) followed by sodium triacetoxyborohydride (184 mg). The mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (400 mL) and washed with 2N aqueous NaOH, water, and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and evaporation of the solvent gave the title compound.

Example 363D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[2-(cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 363C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.35 (s, 1H), 8.02 (d, 2H), 7.51 (m, 3H), 7.40 (m, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67

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(dd, 1H), 6.39 (d, 1H), 6.20 (s, 1H), 4.27 (d, 2H), 3.13 (m, 4H), 2.88 (m, 3H), 2.67 (m, 4H), 2.09 (m, 10H), 1.49 (m, 9H), 0.93 (s, 6H), 0.45 (m, 4H).

## Example 364

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 364A

## 6-amino-5-nitropyridine-3-sulfonic acid

6-Aminopyridine-3-sulfonic acid (20 g) in concentrated H<sub>2</sub>SO<sub>4</sub> (80 mL) was heated at 50° C. until it was completely dissolved. To this solution was added fuming HNO<sub>3</sub> slowly over 20 minutes, so the internal temperature did not exceed 55° C. After the addition was complete, the reaction mixture was heated at 50° C. for 1 hour. After it was cooled to room temperature, it was poured into 150 g of ice. The mixture was stirred for another hour. The flask was cooled to 0° C., and was kept at 0° C. for another 2 hours. The solid was collected by filtration, and washed with cold 1:1 water/ethanol (20 mL), followed by diethyl ether (10 mL). The solid was dried in a vacuum oven overnight to provide the title compound.

## Example 364B

## 6-hydroxy-5-nitropyridine-3-sulfonic acid

EXAMPLE 364A (4.0 g) in aqueous HCl (37%, 12 mL) and water (50 mL) was treated with sodium nitrite (1.19 g) in water (8 mL) dropwise at 0° C. After the addition was complete, the reaction mixture was stirred at 0° C. for 1 hour. The mixture was heated at reflux for 2 hours. Water was distilled off to give a dry residue. After the residue was cooled to room temperature, a solution of 1:1 ethano/water (20 mL) was added. The resulting suspension was cooled to 0° C., and kept at 0° C. for 1 hour. The solid was collected by filtration to provide the title compound.

## Example 364C

## 6-chloro-5-nitropyridine-3-sulfonyl chloride

A mixture of EXAMPLE 364B (2.6 g), PCl<sub>5</sub> (5.91 g), and POCl<sub>3</sub> (10 mL) was heated at 120° C. for 4 hours. The initial suspension became a clear solution. The excess of POCl<sub>3</sub> was distilled off. After it was cooled to room temperature, the residue was poured into 50 g of crushed ice. The solid was extracted into ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated to give crude product that was used in the next step without further purification.

## Example 364D

## 6-chloro-5-nitropyridine-3-sulfonamide

EXAMPLE 364C in tetrahydrofuran (10 mL) was cooled to -10° C. To this solution was added concentrated ammonium hydroxide (0.82 mL) dropwise. The solution was stirred at -10° C. for 10 minutes. The solvent was removed under

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pressure at room temperature. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

## Example 364E

## 5-nitro-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 364D for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for (4-fluoro-2H-pyran-4-yl)methanamine in EXAMPLE 138D.

## Example 364F

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 364E for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.93 (s, 1H), 8.73 (d, 1H), 8.69 (d, 1H), 8.00 (d, 1H), 7.54 (d, 1H), 7.47-7.48 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.35 (dd, 1H), 6.22 (d, 1H), 3.83 (dd, 2H), 3.51 (t, 2H), 3.21-3.27 (m, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 1.90-2.27 (m, 12H), 1.58 (dd, 2H), 1.39 (t, 2H), 1.18-1.28 (m, 2H), 0.88-0.93 (m, 8H).

## Example 365

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 365A

## 7-(azidomethyl)-2-oxaspiro[3.5]nonane

To a 250 mL round-bottomed flask was EXAMPLE 351F (350 mg) in tetrahydrofuran (75.0 mL) to give a colorless solution. The solution was cooled to 0° C., triphenylphosphine (2.94 g), diisopropyl azodicarboxylate (2.18 mL) and diphenyl phosphorazidate (2.32 mL) were added and the reaction was stirred for 30 minutes at room temperature. The mixture was concentrated and purified the residue by regular phase flash column chromatography (Analoxig, 0-20% hexanes/ethyl acetate).

## Example 365B

## 2-oxaspiro[3.5]nonan-7-ylmethanamine

To a 50 mL, round-bottomed flask was added 10% palladium on carbon (58.7 mg). The flask was flushed with N<sub>2</sub> and EXAMPLE 365A (400 mg) was added as a methanol solution (10.5 mL). The flask was then flushed several times with H<sub>2</sub>

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(via balloon) and heated to 45° C. for 2 hours. The reaction was cooled to room temperature, filtered through celite and the filtrate was concentrated by rotary evaporation. The residue was used in the next step without further purification.

## Example 365C

4-(2-oxaspiro[3.5]nonan-7-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 365B for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 365D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(2-oxaspiro[3.5]nonan-7-ylmethylamino)-3-nitrophenylsulfonyl)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 365C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H) 11.25-11.49 (m, 1H) 8.48-8.66 (m, 2H) 8.03 (d, 1H) 7.79 (dd, 1H) 7.41-7.61 (m, 3H) 7.27-7.40 (m, 2H) 7.05 (t, 3H) 6.67 (dd, 1H) 6.39 (dd, 1H) 6.18 (d, 1H) 4.29 (s, 2H) 4.19 (s, 2H) 3.17-3.27 (m, 2H) 2.99-3.14 (m, 4H) 2.69-2.79 (m, 2H) 2.09-2.28 (m, 6H) 2.04 (d, 2H) 1.95 (s, 2H) 1.66 (d, 2H) 1.49-1.61 (m, 1H) 1.29-1.45 (m, 4H) 0.93-1.05 (m, 2H) 0.92 (s, 6H).

## Example 366

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-cyano-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 366A

tert-butyl  
(4-cyano-4-methylcyclohexyl)methylcarbamate

To a cooled (−78° C.) solution of tert-butyl (4-cyanocyclohexyl)methylcarbamate (500 mg) in tetrahydrofuran (10 mL) was added lithium diisopropylamide (2.0 mL, 2M in heptane). The mixture was stirred at −78° C. for 30 minutes before the addition of CH<sub>3</sub>I (1 mL). The mixture was then stirred and the temperature was allowed to warm to room temperature. The reaction was quenched with aqueous NH<sub>4</sub>Cl and the mixture was extracted with ethyl acetate (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent and silica gel chromatography (40% ethyl acetate in hexane) of the crude material gave the title compound.

## Example 366B

4-(aminomethyl)-1-methylcyclohexanecarbonitrile

To a solution of EXAMPLE 366A (480 mg) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 3 hours. The mixture was then

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concentrated under vacuum and was used directly in the next reaction without further purification.

## Example 366C

4-((4-cyano-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-3-nitrobenzenesulfonamide (362 mg) in tetrahydrofuran (10 mL) was added EXAMPLE 366B (250 mg) and N,N-diisopropylethylamine (2 mL). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 366D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-cyano-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 366C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H) 11.37 (m, 1H) 8.59 (m, 2H) 8.04 (d, 1H) 7.80 (d, 1H) 7.51 (m, 3H) 7.34 (d, 2H) 7.10 (d, 1H) 7.04 (d, 2H) 6.68 (dd, 1H) 6.39 (m, 1H) 6.19 (s, 1H) 3.07 (m, 4H) 2.75 (m, 2H) 2.17 (m, 7H) 1.76 (m, 9H) 1.32 (m, 9H) 0.92 (s, 6H).

## Example 367

{[4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-([4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)amino}methyl pivalate

This example was prepared by substituting chloromethyl pivalate for chloromethyl butyrate in EXAMPLE 368. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.72 (s, 1H) 8.43 (d, 1H) 8.22 (dd, 1H) 8.01 (d, 1H) 7.55 (m, 3H) 7.36 (m, 3H) 7.03 (d, 2H) 6.68 (dd, 1H) 6.41 (m, 1H) 6.17 (d, 1H) 5.83 (s, 2H) 4.40 (d, 2H) 3.78 (m, 2H) 3.59 (m, 2H) 3.08 (br m, 4H) 2.73 (br s, 2H) 2.18 (br m, 6H) 1.96 (s, 2H) 1.84 (m, 4H) 1.39 (m, 2H) 1.00 (s, 9H) 0.92 (s, 6H).

## Example 368

{[4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-([4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)amino}methyl butyrate

EXAMPLE 37E (500 mg) was dissolved in acetonitrile (3.7 mL) and chloromethyl butyrate (77 mg) and Hunig's base (73 mg) were added. The reaction was heated under reflux for one day. After cooling and dilution with dimethylsulfoxide (4 mL) the reaction was purified by preparative HPLC using a 250×50 mm C18 column and eluting with 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 mL) and washed



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with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.72 (s, 1H), 8.43 (d, 1H), 8.22 (dd, 1H), 8.01 (d, 1H), 7.55 (m, 3H), 7.36 (m, 3H), 7.03 (d, 2H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.17 (d, 1H), 5.83 (s, 2H), 4.40 (d, 2H), 3.78 (m, 2H), 3.59 (m, 2H), 3.08 (br m, 4H), 2.73 (br s, 2H), 2.18 (m, 8H), 1.96 (s, 2H), 1.84 (m, 4H), 1.39 (m, 4H), 0.92 (s, 6H), 0.75 (t, 3H).

## Example 369

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(2H<sub>8</sub>)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 369A

methyl 4-[(2,2,3,3,5,5,6,6-<sup>2</sup>H<sub>8</sub>)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoate

Into a 40 mL vial were added EXAMPLE 3H (1.55 g) and piperazine-d<sub>8</sub> (2.040 g) in dimethylsulfoxide (13 mL). The solution was heated to 85° C. for 2.5 hours, and was then allowed to cool to room temperature overnight. The mixture was transferred to a 120 mL flask and was cooled to 5-10° C. Dichloromethane (30 mL) was added, then water (10 mL) was added via syringe over 5 minutes maintaining temp at no more than 15° C. The layers were separated and the organic layer was washed with water (4×10-15 mL) until pH of aqueous layer was 8-9. The organic layer was filtered through Na<sub>2</sub>SO<sub>4</sub> and rinsed with dichloromethane (5 mL), and concentrated to provide the title compound.

## Example 369B

methyl 4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(2H<sub>8</sub>)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoate

In a 100 mL round-bottomed flask, EXAMPLE 369A (3.4 g), EXAMPLE 290B (1.321 g) and dichloromethane (3 mL) were added to a 100 mL round bottom flask at room temperature. To a separate 50 mL 3 neck round bottom flask, sodium triacetoxymethylborohydride (1.330 g) and dichloromethane (12 mL) were added to give a slurry. After cooling the 50 mL round bottom flask to 18-20° C., the piperazine adduct/aldehyde solution was added via syringe over 5 minutes. The triacetoxymethylborohydride gradually dissolved to give a clear solution after ~5 minutes. After an additional 10 minutes, the solution became hazy. After 16 hours, the reaction was cooled to 5-10° C. Saturated aqueous NaHCO<sub>3</sub> (12 mL) was added over 5 minutes maintaining the temperature at no more than 10° C. The layers were separated and the organic layer was washed with saturated aqueous NaHCO<sub>3</sub>, and 10% NaCl (12 mL), and then filtered through Na<sub>2</sub>SO<sub>4</sub> and rinsed with dichloromethane (4 mL). The solution was concentrated on a rotovap, and chase concentrated with methanol (40 mL). The resulting solution was cooled to 5-10° C., and the product precipitated. The solution was mixed at room temperature for 30 minutes, then filtered and rinsed with methanol (5 mL), and the product was air dried.

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## Example 369C

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(2H<sub>8</sub>)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 369B for EXAMPLE 15G in EXAMPLE 15H.

## Example 369D

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(2H<sub>8</sub>)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a mixture of EXAMPLE 369C (2.0 g), EXAMPLE 1F (1.1 g) and N,N-dimethylpyridin-4-amine (0.7 g) in dichloromethane (20 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.8 g). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with N,N-dimethylethane-1,2-diamine (0.6 g) and stirred at room temperature for 3 hours. The mixture was extracted with 20% aqueous acetic acid and washed with 5% aqueous NaCl. Methanol (2 mL) and ethyl acetate (18 mL) were added and the precipitate was collected by filtration to provide the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.37 (s, br, 1H), 8.60 (t, 1H), 8.55 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47-7.54 (m, 3H), 7.31-7.34 (m, 2H), 7.09 (d, 1H), 7.01-7.03 (m, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.83 (dd, 2H), 3.21-3.30 (m, 4H), 3.00-3.10 (s, 4H), 2.75 (s, 2H), 2.05-2.24 (m, 6H), 1.95 (s, 2H), 1.80-1.93 (m, 1H), 1.55-1.64 (m, 2H), 1.37 (t, 2H), 1.18-1.31 (m, 2H), 0.90 (s, 6H).

## Example 370

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl}benzamide

## Example 370A

5-amino-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

A mixture of EXAMPLE 364E (0.16 g) and 5% palladium on carbon (0.025 g) in ethanol (5 mL) was treated with a balloon of hydrogen. The reaction mixture was stirred overnight. The solid was filtered off. The filtrate was concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

## Example 370B

3-((tetrahydro-2H-pyran-4-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridine-6-sulfonamide

EXAMPLE 370A (0.085 g) in water (10 mL) was treated with concentrated H<sub>2</sub>SO<sub>4</sub> (0.5 mL). The solution was cooled to 0° C. To this solution was added NaNO<sub>2</sub> (0.023 g) in water (1 mL) dropwise. The solution was stirred for 1 hour at 0° C. The reaction mixture was poured into saturated NaHCO<sub>3</sub> solution, and extracted with ethyl acetate three times. The

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combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated to give the title compound.

**Example 370C**

2-((1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-((tetrahydro-2H-pyran-4-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylsulfonyl)benzamide

This example was prepared by substituting EXAMPLE 370B for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.60 (s, 1H), 9.11 (s, 1H), 8.92 (d, 1H), 7.96 (d, 1H), 7.55 (d, 1H), 7.45-7.46 (m, 1H), 7.42 (s, 1H), 7.36 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.32 (s, 1H), 6.22 (s, 1H), 4.63 (d, 2H), 3.80 (dd, 2H), 3.21-3.30 (m, 2H), 3.16 (s, 4H), 2.83 (s, 2H), 2.19-2.29 (m, 6H), 1.97 (s, 2H), 1.33-1.41 (m, 6H), 0.93 (s, 2H).

**Example 371**

4-((4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((6-((trans-4-hydroxy-4-methylcyclohexyl)methyl)amino)-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 371A**

6-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 364D for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 376B for EXAMPLE 138C in EXAMPLE 138D. The title compound was isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5  $\mu\text{L}$ , C18(2), 250 $\times$ 21.20 mm, 5  $\text{\AA}$ ) eluting with 20-80% acetonitrile in water with 0.1% TFA.

**Example 371B**

4-((4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((6-((trans-4-hydroxy-4-methylcyclohexyl)methyl)amino)-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 371A for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.63 (s, 1H), 11.53-10.99 (m, 1H), 8.91 (s, 1H), 8.71 (dd, 2H), 8.01 (d, 1H), 7.61-7.44 (m, 3H), 7.44-7.28 (m, 2H), 7.12-6.97 (m, 2H), 6.76-6.61 (m, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 3.92 (s, 1H), 3.48 (t, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.24 (dd, 6H), 1.96 (s, 2H), 1.37 (ddd, 11H), 1.07 (s, 3H), 0.93 (s, 6H).

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4-((4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-((5-cyano-6-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 372A**

ethyl  
4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

To 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.00 g) was added HCl (4.0M in dioxane, 4.54 mL). After 1 hour the reaction was concentrated and dried under high vacuum. The resulting solid was dissolved in dichloromethane (5 mL) and treated with sodium triacetoxyborohydride (1.155 g) and oxetan-3-one (0.262 g) and stirred overnight. The reaction was quenched with saturated  $\text{NaHCO}_3$  solution (20 mL) and extracted into dichloromethane (2 $\times$ 25 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting with a gradient of 0.5% to 3.75% methanol/dichloromethane over 40 minutes (flow=30 mL/minute) gave the title compound.

**Example 372B**

(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

To a solution of EXAMPLE 372A (0.59 g) in tetrahydrofuran (5 mL) was added lithium aluminum hydride (1.80 mL) at 0 $^\circ$  C. The reaction was removed from the ice bath and allowed to warm to room temperature. The reaction was quenched by the dropwise addition of 0.6 mL of water followed by 0.2 mL of 2N aqueous NaOH. The reaction was filtered through diatomaceous earth and rinsed with ethyl acetate (50 mL). The organics were concentrated and loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minute (flow=40 mL/minutes) to give the title compound.

**Example 372C**

5-bromo-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 372B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

**Example 372D**

5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 372C for EXAMPLE 36B in EXAMPLE 36C.

**Example 372E**

2-((1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 372D for EXAMPLE 11B in EXAMPLE 11D.

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<sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.71 (s, 1H), 8.52 (s, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.48-7.30 (m, 4H), 7.06 (d, 2H), 6.68 (d, 1H), 6.37-6.22 (m, 2H), 4.65-4.40 (m, 6H), 3.58 (s, 1H), 3.12 (s, 6H), 2.84-2.59 (m, 4H), 2.17 (s, 6H), 1.96 (d, 6H), 1.41 (s, 2H), 0.93 (s, 6H).

## Example 373

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide

## Example 373A

morpholine-4-carboxamide

A solution of morpholine-4-carbonyl chloride (2.0 g) in methanol (10 mL) and 7 N NH<sub>3</sub> in methanol (5 mL) was stirred at 45° C. overnight. The mixture was concentrated to give a solid, which was dried under vacuum.

## Example 373B

N-(2-nitro-4-sulfamoylphenyl)morpholine-4-carboxamide

This example was prepared by substituting EXAMPLE 373A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 373C

N-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenyl)morpholine-4-carboxamide

This example was prepared by substituting EXAMPLE 373B for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (s, 1H), 10.41 (s, 1H), 9.27 (d, 1H), 8.81 (d, 1H), 8.50 (dd, 1H), 8.40 (d, 1H), 8.09 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.67 (m, 4H), 3.58 (m, 4H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 374

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(methoxymethyl)cyclohexyl]methyl}amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 374A

(4,4-diethoxycyclohexyl)methanol

Ethyl 4,4-diethoxycyclohexanecarboxylate (6.67 g) synthesized according to a literature procedure (*European Journal of Organic Chemistry*, 2008, 5, 895) in tetrahydrofuran (60 mL) was treated with 2 M lithium aluminum hydride in tetrahydrofuran (14.5 mL) at 0° C. for 1 hour. Water (3 mL) was slowly added to quench the reaction. The precipitates

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were filtered off and washed with ethyl acetate. The filtrate was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

## Example 374B

1,1-diethoxy-4-(methoxymethyl)cyclohexane

EXAMPLE 374A (665 mg) in tetrahydrofuran (20 mL) was treated with NaH (394 mg) for 30 minutes and then CH<sub>3</sub>I (0.267 mL) was slowly added. The resulting mixture was stirred overnight and the reaction was quenched with a few drops of water. The mixture was concentrated and the residue was suspended in water and extracted with dichloromethane. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography, and was eluted with 0-15% ethyl acetate in dichloromethane to provide the title compound.

## Example 374C

4-(methoxymethyl)cyclohexanone

EXAMPLE 374B (2.2 g) in a mixture of water (3 mL) and acetic acid (12 mL) was heated at 65° C. for 2 hours. The reaction mixture was concentrated. The residue was mixed with water and saturated aqueous NaHCO<sub>3</sub> and extracted with dichloromethane. The dichloromethane layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

## Example 374D

4-(methoxymethyl)cyclohexanecarbonitrile

To a cold (-10° C.) solution of EXAMPLE 374C (1.18 g) and toluenesulfonylmethyl isocyanide (2.268 g) in dimethoxyethane (3 mL) and absolute ethanol (0.1 mL) was added (in small portions) potassium tert-butoxide (2.235 g). The reaction mixture was continued to stir at <5° C. for 30 minutes, warmed to room temperature, heated at 35° C. for 30 minutes and then at room temperature for 2 hours. The reaction mixture was concentrated and the residue was dissolved in water-brine, and extracted with dichloromethane. The dichloromethane layer was purified by flash chromatography, and was eluted with 5% ethyl acetate in dichloromethane to provide the title compound.

## Example 374E

(4-(methoxymethyl)cyclohexyl)methanamine

To a solution of EXAMPLE 374D (460 mg) in tetrahydrofuran (15 mL) was added 2M lithium aluminum hydride in tetrahydrofuran (2.252 mL) slowly. The reaction mixture was stirred at room temperature for 1 hour, refluxed for 1 hour and cooled. 2 mL of 2M aqueous NaOH and water (5 mL) was added. The solid was filtered off and washed with ether. The filtrate was concentrated. The residue was mixed with dichloromethane (50 mL) and the resulting mixture was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to provide the title compound.

## Example 374F

4-((4-(methoxymethyl)cyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 374E (450 mg) and 4-fluoro-3-nitrobenzenesulfonamide (693 mg) in tetrahydrofuran (10 mL) were

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stirred overnight. The reaction mixture was concentrated and the residue was suspended in a mixture of CH<sub>3</sub>CN, methanol and water. The precipitates were collected, washed with water and dried to give the title compound.

## Example 374G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((4-(methoxymethyl)cyclohexyl)methylamino)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 374F in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.40 (s, 1H), 8.53-8.61 (m, 2H), 8.04 (d, 1H), 7.77-7.82 (m, 1H), 7.47-7.55 (m, 3H), 7.34 (d, 2H), 7.02-7.09 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.18-3.27 (m, 5H), 3.04-3.14 (m, 5H), 2.75 (s, 2H), 2.11-2.24 (m, 6H), 1.95 (s, 2H), 1.69-1.84 (m, 3H), 1.33-1.63 (m, 7H), 0.84-1.05 (m, 9H).

## Example 375

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(5-chloro-6-([1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 375A

methyl 1-(thiazol-2-yl)piperidine-4-carboxylate

A mixture of methyl piperidine-4-carboxylate (2.045 g), 2-bromothiazole (1.64 g), and Cs<sub>2</sub>CO<sub>3</sub> (5.86 g) in dimethylformamide (15 mL) was heated at 100° C. overnight. After it cooled to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

## Example 375B

(1-(thiazol-2-yl)piperidin-4-yl)methanol

This example was prepared by substituting EXAMPLE 375A for EXAMPLE 339A in EXAMPLE 339B.

## Example 375C

5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 375B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

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## Example 375D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

This example was prepared by substituting EXAMPLE 375C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.49 (s, 1H), 8.17 (s, 1H), 8.01 (d, 1H), 7.54 (d, 1H), 7.48-7.49 (m, 2H), 7.35 (d, 2H), 7.14 (d, 1H), 7.05 (d, 2H), 6.80 (d, 1H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.28 (d, 2H), 3.92 (d, 2H), 2.98-3.10 (m, 6H), 2.86 (s, 2H), 2.30 (m, 4H), 2.03-2.15 (m, 3H), 1.96 (s, 2H), 1.96 (s, 2H), 1.82-1.86 (m, 2H), 1.33-1.44 (m, 4H), 0.93 (s, 6H).

## Example 376

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(6-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino)-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 376A

tert-butyl  
(4-hydroxy-4-methylcyclohexyl)methylcarbamate

A solution of tert-butyl (4-oxocyclohexyl)methylcarbamate (1.00 g) was dissolved in tetrahydrofuran (20 mL) and cooled to -78° C. Methylmagnesium bromide (4.40 mL) was added dropwise. The reaction was stirred for 2 hours at -78° C. then allowed to warm to 0° C. and stirred for 30 minutes. The resulting suspension was quenched with water (10 mL), diluted with ether (50 mL), washed with ammonium chloride (25 mL), washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting using a gradient of 5% to 50% ethyl acetate/dichloromethane over 30 minutes (flow=60 mL/min) gave the title compound as a ~2:1 mixture of cis and trans isomers.

## Example 376B

4-(aminomethyl)-1-methylcyclohexanol

To a solution of EXAMPLE 376A (0.75 g) in dichloromethane (3 mL) was added a few drops of water followed by trifluoroacetic acid (1.19 mL) and the reaction stirred at room temperature. After stirring for 2 h added additional trifluoroacetic acid (0.5 mL). After an additional 4 h the reaction was concentrated and dried under high vacuum. The resulting oily solid was triturated with diethyl ether with sonication. Filtration and washing with diethyl ether gave the title compound as a trifluoroacetic acid salt and a mixture of cis and trans isomers.

## Example 376C

6-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 376D for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 376B for (4-fluorotetrahydro-2H-pyran-4-yl)



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methanamine in EXAMPLE 138D. The title compound was isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 $\mu$ , C18(2), 250 $\times$ 21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% TFA.

## Example 376D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This example was prepared by substituting EXAMPLE 376C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>)  $\delta$  11.64 (s, 1H), 8.91 (s, 1H), 8.72 (d, 1H), 8.70 (d, 1H), 8.01 (d, 1H), 7.47-7.54 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 3.93 (s, 1H), 3.48 (t, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.15-2.33 (m, 6H), 1.96 (s, 1H), 1.34-1.59 (m, 9H), 1.17-1.24 (m, 2H), 1.07 (s, 2H), 0.92 (s, 6H).

## Example 377

4-(4-([2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 378D for EXAMPLE 1E and EXAMPLE 337M for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>)  $\delta$  13.07 (s, 1H), 9.31 (d, 1H), 8.68 (t, 1H), 8.44 (d, 1H), 8.37 (dd, 1H), 8.10 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 6.92 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 3.20 (m, 5H), 3.06 (t, 4H), 2.77 (m, 2H), 2.57 (d, 1H), 2.49 (m, 1H), 2.17 (m, 6H), 1.86 (m, 5H), 1.69 (m, 4H), 1.40 (s, 3H), 1.23 (m, 5H).

## Example 378

4-(4-([2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 378A

2-chloro-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

Dimethylformamide (1.298 mL) in dichloromethane (2.0 mL) at -10° C. was treated dropwise with POCl<sub>3</sub> (1.426 mL) to give a colorless solution. The mixture was stirred 5 minutes and then warmed to room temperature and stirred 30 minutes. The solution was cooled to -10° C., treated dropwise with a solution of 4-methoxy-4-methylcyclohexanone (1.74 g) in

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dichloromethane (2.5 mL), and stirred for 4 hours at ambient temperature. The reaction mixture was poured over a mixture of ice and 25% aqueous sodium acetate solution. After the ice melted, the reaction mixture was poured into a separatory funnel and extracted with diethyl ether (4 $\times$ 125 mL). The diethyl ether extracts were washed with NaHCO<sub>3</sub> solution and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on silica gel with 0 to 5% ethyl acetate in hexanes as the eluent.

## Example 378B

2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

EXAMPLE 378A (1.55 g), 4-chlorophenylboronic acid (1.542 g), PdOAc<sub>2</sub> (0.055 g), K<sub>2</sub>CO<sub>3</sub> (2.84 g) and tetrabutylammonium bromide (2.65 g) were combined in a 50-mL round-bottomed flask equipped with a magnetic stir bar. Water (9.13 mL) was added. The vial was flushed with nitrogen, capped and stirred at 45° C. for 14 hours. The reaction mixture was cooled to room temperature and partitioned between brine and diethyl ether. The organic layer was washed with brine, dried (MgSO<sub>4</sub>), filtered through a plug of celite, concentrated and chromatographed on silica gel with 5 to 20% ethyl acetate in hexanes as the eluent.

## Example 378C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 378B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A except that a small amount of DMSO was added to the reaction mixture.

## Example 378D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 378C for EXAMPLE 15G in EXAMPLE 15H.

## Example 378E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 378D for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>)  $\delta$  13.07 (s, 1H), 9.31 (d, 1H), 8.68 (t, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.09 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 6.90 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 3.97 (dd, 2H), 3.30 (td, 2H), 3.21 (s, 3H), 3.15 (m, 2H), 3.06 (t, 4H), 2.77 (m, 2H), 2.57 (d, 1H), 2.50 (m, 1H), 2.16 (m, 6H), 1.81 (m, 2H), 1.63 (m, 1H), 1.57 (dd, 2H), 1.32 (m, 2H), 1.21 (s, 3H).

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## SEQUENCE LISTING

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&lt;213&gt; ORGANISM: Artificial Sequence

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 1 5 10 15

What is claimed is:

1. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-([1-tetrahydro-2H-pyran-4-yl]piperidin-4-yl)amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([1-methylpiperidin-4-yl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-([tetrahydro-2H-pyran-4-yl]methyl)amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([4-methylpiperazin-1-yl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([4-morpholin-4-yl]cyclohexyl)amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([2-methoxyethyl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-([3S]-tetrahydro-2H-pyran-3-yl]methyl)amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(1,4-dioxan-2-yl]methoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-([3R]-tetra-

rahydro-2H-pyran-3-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([2-methoxyethyl]amino)-3-([trifluoromethyl]sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-([tetrahydro-2H-pyran-4-yl]methyl)amino)-3-([trifluoromethyl]sulfonyl]phenyl)sulfonyl)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-(tetrahydro-2H-pyran-4-yl]methoxy)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([1,4-dioxan-2-yl]methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-([2,2,2-trifluoroethyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-([3,3,3-trifluoropropyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([2S)-1,4-dioxan-2-yl]methoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-methoxycyclohexyl]methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-([2R)-1,4-dioxan-2-yl]methoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-yl)-methoxyphenyl)sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-morpholin-4-ylcyclohexyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-([1-acetyl]piperidin-4-yl)amino)-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([3-morpholin-4-ylpropyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-morpholin-4-ylcyclohexyl]oxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([2-cyanoethyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-({4-([4-bis(cyclopropylmethyl)amino]cyclohexyl]amino)-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-methylpiperidin-4-yl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([morpholin-3-ylmethyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-morpholin-4-yl-

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but-2-ynyl]oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 3-({4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxymethyl)morpholine-4-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([morpholin-3-ylmethoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-(methylsulfonyl)piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1,1-dioxidotetrahydro-2H-thiopyran-4-yl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-chloro-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-([1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-(2,2-difluoroethyl)piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-(1-cyclopropylpiperidin-4-yl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-(morpholin-4-ylcyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-(dicyclopropylamino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-1-tet-

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rahydro-2H-pyran-4-ylpiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cis-3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(4-

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tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-[[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxy]methyl]-4-fluoropiperidine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(4-(4-tetrahydro-2H-pyran-4-ylpiperazin-1-yl)cyclohexyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(4-methylmorpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(2-methoxyethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-[(4-acetylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(4-fluorotetrahy-



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dro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclobutyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(1-(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(methylsulfonyl)piperidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-[(1-(acetyl)piperidin-3-yl)methyl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(methylsulfonyl)pyrrolidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2-fluoro-1-(fluoromethyl)ethyl)azetidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(methylsulfonyl)pyrrolidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-[(1-(acetylpyrrolidin-3-yl)methyl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-[(1-(3R)-1-acetylpyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(1R,3R)-3-hydroxycyclopentyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(1S,3S)-3-hydroxycyclopentyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(1S,3R)-3-hydroxycyclopentyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(1R,3S)-3-hydroxycyclopentyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(1-(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2-fluoro-1-(fluoromethyl)ethyl)azetidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(1-(1-cyclopropyl)piperidin-4-yl)methyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(2-fluoroethyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-[(4-cyclobutyl)morpholin-3-yl]methyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(3-nitro-4-[(4-tetrahydrofuran-3-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-([1-(2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-([1-(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(4-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(3-nitro-4-([3-(trifluoromethoxy)benzyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(3-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-([4-(difluoromethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-([1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-[(4-([4-(acetylamino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-([[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-([[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-([[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(4-([[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-[(3-nitro-4-([[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(4-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-N-({4-[(3-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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rolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-[(2-methoxyethoxy)ethyl]morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyanomethyl)morpholin-2-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(N,N-dimethylglycyl)morpholin-2-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

(2-{[(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)amino)methyl]morpholin-4-yl)acetic acid;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-oxetan-3-yl)morpholin-2-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropyl)morpholin-2-yl]methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyr-

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rolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2-methoxyethyl)piperidin-3-yl]methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(3R)-tetrahydrofuran-3-ylamino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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[illegible]

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-[(3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro)-2H-pyran-4-yl]methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(1,3-thiazol-5-yl)methyl]amino}propyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-(cyclopropyl(2.2.2-trifluoroethyl)amino}propyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-[(3-chloro-4-{[1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-(cyclopropyl(oxetan-3-yl)amino}propyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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methyl 2-[[4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl]amino]methyl]morpholine-4-carboxylate;

2-[[4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[4-([4-(methylsulfonyl)morpholin-2-yl]methyl)amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[4-([3-(cyclobutyl(cyclopropyl)amino]propyl)amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[4-([[(2R)-4-cyclopropylmorpholin-2-yl]methyl)amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[4-([[(2S)-4-cyclopropylmorpholin-2-yl]methyl)amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-([4-cyclopropylmorpholin-2-yl]methoxy)phenyl]sulfonyl)-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-([4-cyclopropylmorpholin-2-yl]methyl)amino]phenyl]sulfonyl)-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-[[2-chloro-4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[4-([4-(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl)amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[4-([4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[4-([4-(2,2-difluorocyclopropyl)amino]cyclohexyl)amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([trans-4-hydroxy-4-methylcyclohexyl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([4-(4-cyclopropylmorpholin-2-yl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([3-cyano-4-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([trans-4-ethyl-4-hydroxycyclohexyl]methyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([cis-4-ethyl-4-hydroxycyclohexyl]methyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([3-nitro-4-([[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl]amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([3-chloro-4-([trans-4-hydroxy-4-methylcyclohexyl]methoxy)phenyl]sulfonyl)-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([4-(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([3-nitro-4-([2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([4-(4-cyano-4-methylcyclohexyl]methyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)morpholine-4-carboxamide; and

4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-[[4-([4-(methoxymethyl)cyclohexyl]methyl)amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

2. Trans-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([4-(morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

3. Cis-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([4-(methoxycyclohexyl]methyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

4. Trans-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl-N-([4-([4-(methoxy-

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cyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

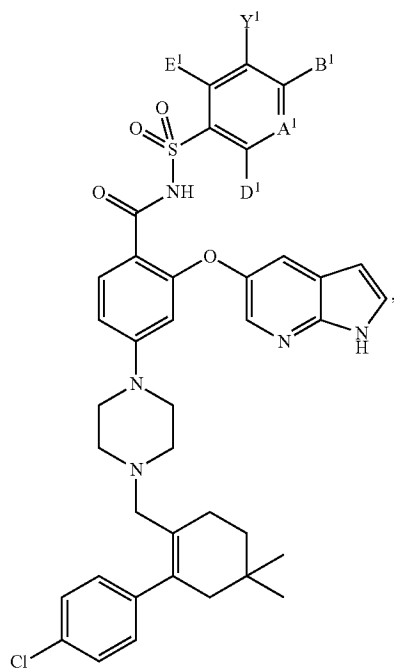
5. 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

6. 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

7. 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

8. 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino)propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

9. A compound having Formula (III)



or a pharmaceutically acceptable salt thereof, wherein

A<sup>1</sup> is C(A<sup>2</sup>);

A<sup>2</sup> is H, F, Br, I, or Cl;

B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Br, I, or Cl;

D<sup>1</sup> is H, F, Br, I, or Cl;

E<sup>1</sup> is H; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>;

R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>;

R<sup>4</sup> is cycloalkyl or heterocycloalkyl;

R<sup>5</sup> is alkyl or alkynyl, each of which is unsubstituted or substituted with one or two or three substituents independently selected from the group consisting of R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, CN, OH, F, Cl, Br, and I;

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R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, or R<sup>11</sup>;

R<sup>8</sup> is phenyl;

R<sup>9</sup> is heteroaryl;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R<sup>10A</sup>; R<sup>10A</sup> is heteroarene;

R<sup>11</sup> is alkyl, which is unsubstituted or substituted with one or two or three substituents independently selected from the group consisting of R<sup>12</sup>, OR<sup>12</sup>, and CF<sub>3</sub>;

R<sup>12</sup> is R<sup>14</sup> or R<sup>16</sup>;

R<sup>14</sup> is heteroaryl;

R<sup>16</sup> is alkyl;

R<sup>17</sup> is alkyl or alkynyl, each of which is unsubstituted or substituted with one or two or three substituents independently selected from the group consisting of R<sup>22</sup>, F, Cl, Br and I;

R<sup>22</sup> is heterocycloalkyl;

wherein the cyclic moieties represented by R<sup>4</sup>, R<sup>8</sup>, R<sup>10</sup>, and R<sup>22</sup>, are independently unsubstituted or substituted with one or two or three or four or five substituents independently selected from the group consisting of R<sup>57A</sup>, R<sup>27</sup>, OR<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, C(O)OR<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NHS(O)<sub>2</sub>R<sup>57</sup>, OH, CN, (O), F, Cl, Br and I;

R<sup>57A</sup> is spiroalkyl or spiroheteroalkyl;

R<sup>57</sup> is R<sup>58</sup>, R<sup>60</sup>, or R<sup>61</sup>;

R<sup>58</sup> is phenyl;

R<sup>60</sup> is cycloalkyl or heterocycloalkyl;

R<sup>61</sup> is alkyl, which is unsubstituted or substituted with one or two or three substituents independently selected from the group consisting of R<sup>62</sup>, OR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, C(O)OH, CN, F, Cl, Br, and I;

R<sup>62</sup> is R<sup>65</sup> or R<sup>66</sup>;

R<sup>65</sup> is cycloalkyl or heterocycloalkyl;

R<sup>66</sup> is alkyl, which is unsubstituted or substituted with OR<sup>67</sup>;

R<sup>67</sup> is alkyl;

wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, and R<sup>60</sup> are unsubstituted or substituted with one or two or three or four substituents independently selected from the group consisting of R<sup>68</sup>, F, Cl, Br, and I;

R<sup>68</sup> is R<sup>71</sup> or R<sup>72</sup>;

R<sup>71</sup> is heterocycloalkyl; and

R<sup>72</sup> is alkyl, which is unsubstituted or substituted with one or two F.

10. The compound of claim 9, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino)propyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

11. The compound of claim 9, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylmorpho-

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lin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

12. The compound of claim 9, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino}phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-{[3-(cyclopropyl(oxetan-3-yl)amino)propyl]amino}-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

13. The compound of claim 9, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

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14. 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

15. 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

16. The compound of claim 9, or pharmaceutically acceptable salt thereof, wherein

A<sup>1</sup> is C(A<sup>2</sup>);

A<sup>2</sup> is H;

B<sup>1</sup> is NHR<sup>1</sup>;

D<sup>1</sup> is H;

E<sup>1</sup> is H; and

Y<sup>1</sup> is NO<sub>2</sub>.

17. The compound of claim 9, or pharmaceutically acceptable salt thereof, wherein Y<sup>1</sup> is SO<sub>2</sub>R<sup>12</sup> and R<sup>17</sup> is alkyl.

18. The compound or pharmaceutically acceptable salt of claim 9, 16 or 17, wherein R<sup>5</sup> is alkyl.

19. 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising an excipient and the compound or pharmaceutically acceptable salt of any one of claims 1, 2-5, 6, 7, 8, 10, 11, 12, 13, 14, and 15-17.

21. A pharmaceutical composition comprising 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof, and an excipient.

22. 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

23. A pharmaceutical composition comprising 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide and an excipient.

24. A pharmaceutical composition comprising an excipient and the compound or pharmaceutically acceptable salt of claim 18.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,546,399 B2  
APPLICATION NO. : 12/787682  
DATED : October 1, 2013  
INVENTOR(S) : Bruncko et al.

Page 1 of 1

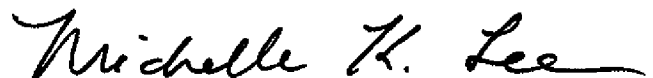
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b)  
by 397 days.

Signed and Sealed this  
Third Day of March, 2015

A handwritten signature in black ink, reading "Michelle K. Lee". The signature is fluid and cursive, with the first letters of each name being capitalized and prominent.

Michelle K. Lee  
*Deputy Director of the United States Patent and Trademark Office*



UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,546,399 B2  
APPLICATION NO. : 12/787682  
DATED : October 1, 2013  
INVENTOR(S) : Bruncko et al.

Page 1 of 5

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

Column 42, line 64 and column 43, line 17, in each occurrence “quaternized” should be --quaternized--.

Column 46, line 15, “non-radio active” should read --non-radioactive--; line 29, “Czajka D M” should read --Czajka D M--.

Column 165, line 50, “bucally” should read --buccally--.

Column 167, line 04, “etinoids/deltoids” should read --retinoids/deltoids--.

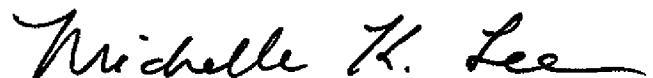
Column 168, line 05, “decarbazine” should read --dacarbazine--; line 09, “rofosfamide” should read --trofosfamide--; line 27, “ethnylcytidine” should read --ethynylcytidine--.

Column 169, line 05, “petuzumab” should read --pertuzumab--; line 06, “(ionafarnib)” should read --(lonafarnib)--; line 09, “bispecfic” should read --bispecific--; line 67, “(pegaptamib)” should read --(pegaptanib)--.

Column 170, line 08, “epirbucin” should read --epirubicin--; line 09, “glarbuicin” should read --galarubicin--; line 16, “(dexrazoxine)” should read --(dexrazoxane)--; line 20, “pirarbucin” should read --pirarubicin--; line 27, “trastuzimab” should read --trastuzumab--; line 38, “(megesterol)” should read --(megestrol)--; line 41, “rilostane” should read --trilostane--; line 46, “lexacalcitrol” should read --lexacalcitol--; line 47, “(aliretinoin)” should read --(alitretinoin)--; line 65, “decarbazine” should read --dacarbazine--.

Column 171, line 04, “sargaramostim” should read --sargramostim--; line 21, “(ratitrexed)” should read --(raltitrexed)--; lines 46 and 54, in each occurrence “combreastatin” should read

Signed and Sealed this  
Seventh Day of April, 2015



Michelle K. Lee  
*Director of the United States Patent and Trademark Office*

**CERTIFICATE OF CORRECTION (continued)**

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--combretastatin--; line 61, “(epithilone B)” should read --(epothilone B)--; line 65, detailed description: “histerelin” should read --histrelin--.

Column 172, line 20, the word “temilifene” should be deleted; line 31, “(zolendronic acid)” should read --(zoledronic acid)--.

Column 181, line 32, column 186, line 61, column 187, line 10, column 188, line 10, and column 190, line 13, in each occurrence “dependant” should read --dependent--.

Column 204, line 04, “trophobalstic” should read --trophoblastic--; line 40, “Burkitts” should read --Burkitt’s--; line 55, “alopecia greata” should read --alopecia areata--; line 59, “abetalipoprotemia” should read --abetalipoproteinemia--.

Column 205, line 14, “hypoglycaemia” should read --hypoglycemia--; line 24, “choleosatatis” should read --cholestasis--; line 31, “hypogammaglobulinaemia” should read --hypogammaglobulinemia--; line 62, “hairy cell leukemia, hairy cell leukemia” should be --hairy cell leukemia--; line 63, “Hallerrorden-Spatz” should read --Hallervorden-Spatz--; line 64, “hemachromatosis” should read --hemochromatosis--.

Column 206, line 07, “leucopaenia” should read --leucopenia--; line 17, “lipidema” should read --lipidemia--; line 18, “lymphedema” should read --lymphedema--; line 29, “myelodyplastic” should read --myelodysplastic--; line 36, “orchitis/epidydimitis” should read --orchitis/epididymitis--; line 53, “supranucleo Palsy” should read --supranuclear palsy--; line 58, “Raynoud’s disease” should read --Raynaud’s disease--; line 66, “Sjorgren’s syndrome” should read --Sjögren’s syndrome--.

Column 207, line 03, “spondyloarthropathy, spondyloarthopathy” should read --spondyloarthropathy--; line 27, “hemaphagocytic” should read --hemophagocytic--.

Column 269, line 66, column 306, line 21, column 367, line 11 and column 416, line 15, in each occurrence the phrase “filtered though” should read --filtered through--.

Column 276, line 53, “GraceResolv” should be --GRACERESOLV--; line 56, “analogix” should be --ANALOGIX--.

Column 278, line 06, “GraceResolve” should be --GRACERESOLV--.

Column 279, line 15, “(1-ethoxycyclopropoxy)trimethysilane” should read --(1-ethoxycyclopropoxy)trimethylsilane--.

Column 283, line 12, “isoproxide” should read --isopropoxide--.

Column 317, line 02, the phrase “allowed to stirred” should read --allowed to stir--.

Column 335, line 25, “cyanoborohyde” should read --cyanoborohydride--.

**CERTIFICATE OF CORRECTION (continued)**

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**U.S. Pat. No. 8,546,399 B2**

Column 357, line 66 and column 415, line 16, in each occurrence “partitioned” should read --partitioned--.

Column 412, line 61, “over night” should read --overnight--.

Column 436, line 36, “Reveris” should be --REVELERIS--.

Column 464, line 19, “N-fluorobenzenesulformimide” should read --N-fluorobenzenesulfonimide--;  
line 40, “analogs” should be --ANALOGIX--.

Column 479, line 40, “ethano/water” should read --ethanol/water--.

**In the Claims**

**CLAIM 1:**

Column 493, line 33, add a “(” to the part reading “4-[1-tetrahydro” to read --4-[(1-tetrahydro--;  
line 50, delete a “(” from the part reading “4-([2-(4-chlorophenyl)” to read  
--4-[2-(4-chlorophenyl)--.

Column 495, line 05, add a “)” to the part reading “(4-chlorophenyl-4,4-dimethylcyclohex” to read  
--(4-chlorophenyl)-4,4-dimethylcyclohex--; line 28, change the first “(” in the part reading  
“{2-(4-chlorophenyl)” to a “[” to read --{2-(4-chlorophenyl)--; line 48, “[2,3-h]” should be  
--[2,3-b]--; line 54, change the first “(” in “{2-(4-chlorophenyl)” to a “[” to read  
--[2-(4-chlorophenyl)--.

Column 496, line 33, add a “)” to the part reading “piperazin-1-yl-2” to read --piperazin-1-yl)-2--;  
line 46, change the “]” in the part reading “piperazin-1-yl]” to read --piperazin-1-yl)--.

Column 497, line 19, add a “{” to the part reading “[4-[(1S,3R)” to read --[(4-{[(1S,3R)--.

Column 498, line 01, add a “(” before the word “tetrahydro” to read as --(tetrahydro--; line 19,  
change the “(” in “{4-(4-tetrahydro” to a “[” to read --{4-(4-tetrahydro--; line 34, add a “{”  
to the part reading “[3R)” to read as --{[(3R)--; line 38, add a “)” to the part reading  
“(4-chlorophenyl)” to read as --(4-chlorophenyl)--; line 62; replace the “(” in the part “([trans” with  
a “{” to read as --{[trans--.

Column 499, line 13, switch the order of the “{” and “(” in the part reading  
“N-[4-([1-(2,2-dimethyltetrahydro” to read as --N-[(4-[1-(2,2-dimethyltetrahydro--; line 61,  
insert --4-- into the part reading “sulfonyl)-4-([2-(4-chlorophenyl)” to read  
--sulfonyl)-4-(4-[2-(chlorophenyl)--.

**CERTIFICATE OF CORRECTION (continued)**

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Column 500, line 30, replace the part reading “4-(4 (2-(4-chlorophenyl))” to read --4-(4-{[2-(4-chlorophenyl)]--; line 47, replace the part reading “piperazin-{[4-(4-(2,2-difluoroethyl))” to read --piperazin-1-yl)-N-{[4-(4-(2,2-difluoroethyl)]--.

Column 501, line 12, remove the “]” in “piperazin-1]-yl)” to read --piperazin-1-yl)--.

Column 503, line 04, add a “{” to the part reading “[1R,4R,5R,6S)” to read as --{[1R,4R,5R,6S)--; line 14, change the “(” in the part reading “([2-(4-chlorophenyl))” to a “{” to read --{[2-(4-chlorophenyl)]--.

Column 504, line 21, change the “(” in the part reading “[2-(4-chlorophenyl))” to a “[” to read --{[2-(4-chlorophenyl)]--; line 25, add a “[” to the part reading “N-{4-([1-(2-methoxyethyl))” to read --N-{4-([1-(2-methoxyethyl)]--; line 29, replace the part “4-(4 (2-(4-chlorophenyl))” with --4-(4-{[2-(4-chlorophenyl)]--; line 61, add a “[” before the part “(3R)-tetrahydrofuran” to read --[(3R)-tetrahydrofuran--.

Column 505, line 12, change the “(” in the part “N-{4-([4-(1,3-difluoropropan))” to a “[” to read --N-{4-([4-(1,3-difluoropropan)]--; line 56, remove the first “(” in “[4-fluoro)” to read --[4-fluoro--.

Column 506, line 16, remove the “)” in “fluorotetrahydro)” to be --fluorotetrahydro--; line 43, “(cyclopropyl(2,2,2-trifluoroethyl))” should read --(cyclopropyl(2,2,2-trifluoroethyl)--; line 56, change the “(” in the part reading “(cyclopropyl)” to a “[” to read --[cyclopropyl--; line 64, add a “{” to the part reading “N-(3,4-difluoro)” to read --N-{(3,4-difluoro--.

Column 507, line 05, the part reading “2-{[4-(4-{[2-(4-chlorophenyl))” should read --2-{[4-([4-(4-{[2-(4-chlorophenyl)]--; following line 49, insert the compound name: --4-(4-{[2-(4-chlorophenyl)]-4,4-dimethylcyclohex-1-en-1-yl)methyl} piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;--.

Column 507, line 57, “methylcyclohex)” should read --methylcyclohexyl)--.

Column 508, line 13, remove the “(” to the part reading “[2-(4-chlorophenyl))” to be --{[2-(4-chlorophenyl)]--.

CLAIM 9:

Column 510, line 22, “R<sup>27</sup>” should read --R<sup>57</sup>--.

CLAIM 10:

Column 510, line 55, replace the “(” in the part “(cyclopropyl)” to read --[cyclopropyl--.



**CERTIFICATE OF CORRECTION (continued)**

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CLAIM 13:

Column 511, line 48, “(4-chlorphenyl)” should read --(4-chlorophenyl)--.

CLAIM 23:

Column 512, line 45, change the “}” “{3-nitro” to read --{3-nitro--.

CLAIM 24:

Column 512, line 48, “compostition” should be --composition--.

# EXHIBIT B

US009174982B2

(12) **United States Patent**  
**Bruncko et al.**(10) **Patent No.:** **US 9,174,982 B2**(45) **Date of Patent:** **Nov. 3, 2015**(54) **APOPTOSIS-INDUCING AGENTS FOR THE  
TREATMENT OF CANCER AND IMMUNE  
AND AUTOIMMUNE DISEASES**(2013.01); **C07D 209/82** (2013.01); **C07D  
401/14** (2013.01); **C07D 403/12** (2013.01);  
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USPC ..... 514/252.18; 544/362  
See application file for complete search history.(72) Inventors: **Milan Bruncko**, Green Oaks, IL (US);  
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| <b>C07D 471/04</b> | (2006.01) |
| <b>C07D 519/00</b> | (2006.01) |
| <b>A61K 31/496</b> | (2006.01) |

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**ABSTRACT**Disclosed are compounds which inhibit the activity of anti-  
apoptotic Bcl-2 proteins, compositions containing the com-  
pounds and methods of treating diseases during which is  
expressed anti-apoptotic Bcl-2 protein.**7 Claims, No Drawings**

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# **APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE AND AUTOIMMUNE DISEASES**

This application is a divisional of U.S. patent application Ser. No. 12/787,682 filed May 26, 2010, which claims benefit of U.S. Provisional Application No. 61/181,203 filed May 26, 2009, each of which is incorporated herein by reference in its entirety.

## **FIELD OF THE INVENTION**

This invention pertains to compounds which inhibit the activity of Bcl-2 anti-apoptotic proteins, compositions containing the compounds, and methods of treating diseases during which anti-apoptotic Bcl-2 proteins are expressed.

## **BACKGROUND OF THE INVENTION**

Anti-apoptotic Bcl-2 proteins are associated with a number of diseases. There is therefore an existing need in the therapeutic arts for compounds which inhibit the activity of anti-apoptotic Bcl-2 proteins.

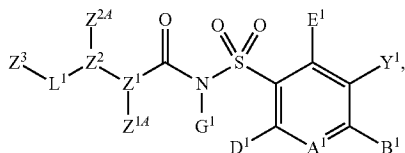
Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system.

Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, spleen cancer, and the like is described in commonly-owned PCT US 2004/36770, published as WO 2005/049593, and PCT US 2004/37911, published as WO 2005/024636.

Involvement of Bcl-2 proteins in immune and autoimmune diseases is described in *Current Allergy and Asthma Reports* 2003, 3, 378-384; *British Journal of Haematology* 2000, 110(3), 584-90; *Blood* 2000, 95(4), 1283-92; and *New England Journal of Medicine* 2004, 351(14), 1409-1418. Involvement of Bcl-2 proteins in arthritis is disclosed in commonly-owned U.S. Provisional Patent Application Ser. No. 60/988,479. Involvement of Bcl-2 proteins in bone marrow transplant rejection is disclosed in commonly-owned U.S. patent application Ser. No. 11/941,196.

## **SUMMARY OF THE INVENTION**

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (I)



wherein

A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC

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(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNH<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

B<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNH<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

D<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNH<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

E<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNH<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, C(O)OH, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, C(O)R<sup>17</sup>, C(O)OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, NH<sub>2</sub>, NHR<sup>17</sup>, N(R<sup>17</sup>)<sub>2</sub>, NHC(O)R<sup>17</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>17</sup>, C(O)N(R<sup>17</sup>)<sub>2</sub>, NHS(O)R<sup>17</sup> or NHSO<sub>2</sub>R<sup>17</sup>; or

E<sup>1</sup> and Y<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

(I) A<sup>2</sup>, B<sup>1</sup>, and D<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNH<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

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$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$A^2$ ,  $D^1$ , and  $E^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$A^2$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$D^1$ ,  $E^1$ , and  $Y^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$A^2$  and  $D^1$ , together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$B^1$ ,  $E^1$ , and  $Y^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$G^1$  is H, or  $C(O)OR$ ;

R is alkyl;

$R^1$  is  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$ ;

$R^{1,4}$  is cycloalkyl, cycloalkenyl or cycloalkynyl;

$R^2$  is phenyl, which is unfused or fused with  $R^{2,4}$ ;  $R^{2,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^3$  is heteroaryl, which is unfused or fused with  $R^{3,4}$ ;  $R^{3,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^4$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{4,4}$ ;  $R^{4,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^5$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^6$ ,  $NC(R^{6A})(R^{6B})$ ,  $R^7$ ,  $OR^7$ ,  $SR^7$ ,  $S(O)R^7$ ,  $SO_2R^7$ ,  $NHR^7$ ,  $N(R^7)_2$ ,  $C(O)R^7$ ,  $C(O)NH_2$ ,  $C(O)NHR^7$ ,  $C(O)N(R^7)_2$ ,  $NHC(O)R^7$ ,  $NR^7C(O)R^7$ ,  $NHSO_2R^7$ ,  $NHC(O)OR^7$ ,  $SO_2NH_2$ ,  $SO_2NHR^7$ ,  $SO_2N(R^7)_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)$

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$NHR^7$ ,  $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$ ,  $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^7$ , OH, (O),  $C(O)OH$ ,  $N_3$ , CN,  $NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

$R^6$  is  $C_2$ - $C_5$ -spiroalkyl, each of which is unsubstituted or substituted with OH, (O),  $N_3$ , CN,  $CF_3$ ,  $CF_2CF_3$ , F, Cl, Br, I,  $NH_2$ ,  $NH(CH_3)$  or  $N(CH_3)_2$ ;

$R^{6A}$  and  $R^{6B}$  are independently selected alkyl or, together with the N to which they are attached,  $R^{6C}$ ;

$R^{6C}$  is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one  $CH_2$  moiety unreplaced or replaced with O,  $C(O)$ ,  $CNOH$ ,  $CNOCH_3$ , S,  $S(O)$ ,  $SO_2$  or  $NH$ ;

$R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$  or  $R^{11}$ ;

$R^8$  is phenyl, which is unfused or fused with  $R^{8,4}$ ;  $R^{8,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^9$  is heteroaryl, which is unfused or fused with  $R^{9,4}$ ;  $R^{9,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{10}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{10,4}$ ;  $R^{10,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{11}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{12}$ ,  $OR^{12}$ ,  $SR^{12}$ ,  $S(O)R^{12}$ ,  $SO_2R^{12}$ ,  $C(O)R^{12}$ ,  $CO(O)R^{12}$ ,  $OC(O)R^{12}$ ,  $OC(O)OR^{12}$ ,  $NH_2$ ,  $NHR^{12}$ ,  $N(R^{12})_2$ ,  $NHC(O)R^{12}$ ,  $NR^{12}C(O)R^{12}$ ,  $NHS(O)_2R^{12}$ ,  $NR^{12}S(O)_2R^{12}$ ,  $NHC(O)OR^{12}$ ,  $NR^{12}C(O)OR^{12}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{12}$ ,  $NHC(O)N(R^{12})_2$ ,  $NR^{12}C(O)NHR^{12}$ ,  $NR^{12}C(O)N(R^{12})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{12}$ ,  $C(O)N(R^{12})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{12}$ ,  $C(O)NHSO_2R^{12}$ ,  $C(O)NR^{12}SO_2R^{12}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{12}$ ,  $SO_2N(R^{12})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{12}$ ,  $C(N)N(R^{12})_2$ ,  $CNOH$ ,  $CNOCH_3$ , OH, (O), CN,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ , F, Cl, Br or I;

$R^{12}$  is  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$  or  $R^{16}$ ;

$R^{13}$  is phenyl, which is unfused or fused with  $R^{13,4}$ ;  $R^{13,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{14}$  is heteroaryl, which is unfused or fused with  $R^{14,4}$ ;  $R^{14,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{15}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with  $R^{15,4}$ ;  $R^{15,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{16}$  is alkyl, alkenyl or alkynyl;

$R^{17}$  is  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  or  $R^{21}$ ;

$R^{18}$  is phenyl, which is unfused or fused with  $R^{18,4}$ ;  $R^{18,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{19}$  is heteroaryl, which is unfused or fused with  $R^{19,4}$ ;  $R^{19,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{20}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with  $R^{20,4}$ ;  $R^{20,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{21}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{22}$ ,  $OR^{22}$ ,  $SR^{22}$ ,  $S(O)R^{22}$ ,  $SO_2R^{22}$ ,  $C(O)R^{22}$ ,  $CO(O)R^{22}$ ,  $OC(O)R^{22}$ ,  $OC(O)OR^{22}$ ,  $NH_2$ ,  $NHR^{22}$ ,  $N(R^{22})_2$ ,  $NHC(O)R^{22}$ ,  $NR^{22}C(O)R^{22}$ ,  $NHS(O)_2R^{22}$ ,  $NR^{22}S(O)_2R^{22}$ ,  $NHC(O)OR^{22}$ ,  $NR^{22}C(O)OR^{22}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{22}$ ,  $NHC(O)N(R^{22})_2$ ,  $NR^{22}C(O)NHR^{22}$ ,  $NR^{22}C(O)N(R^{22})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{22}$ ,  $C(O)N(R^{22})_2$ ,  $C(O)NHOH$ ,



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$C(O)NHOR^{22}$ ,  $C(O)NHSO_2R^{22}$ ,  $C(O)NR^{22}SO_2R^{22}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{22}$ ,  $SO_2N(R^{22})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{22}$ ,  $C(N)N(R^{22})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{22}$  is  $R^{23}$ ,  $R^{24}$  or  $R^{25}$ ;

$R^{23}$  is phenyl, which is unfused or fused with  $R^{23A}$ ;  $R^{23A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{24}$  is heteroarene, which is unfused or fused with  $R^{24A}$ ;  $R^{24A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{25}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{25A}$ ;  $R^{25A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$Z^1$  is  $R^{26}$  or  $R^{27}$ ;

$Z^2$  is  $R^{28}$ ,  $R^{29}$  or  $R^{30}$ ;

$Z^{1A}$  and  $Z^{2A}$  are both absent or are taken together to form  $CH_2$ ,  $CH_2CH_2$  or  $Z^{12A}$ ;

$Z^{12A}$  is  $C_2$ - $C_6$ -alkylene having one or two  $CH_2$  moieties replaced by  $NH$ ,  $N(CH_3)$ ,  $S$ ,  $S(O)$  or  $SO_2$ ;

$L^1$  is a  $R^{37}$ ,  $OR^{37}$ ,  $SR^{37}$ ,  $S(O)R^{37}$ ,  $SO_2R^{37}$ ,  $C(O)R^{37}$ ,  $CO(O)R^{37}$ ,  $OC(O)R^{37}$ ,  $OC(O)OR^{37}$ ,  $NHR^{37}$ ,  $C(O)NH$ ,  $C(O)NR^{37}$ ,  $C(O)NHOR^{37}$ ,  $C(O)NHSO_2R^{37}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{37}$ ,  $C(N)NH$ ,  $C(N)NHR^{37}$ ;

$R^{26}$  is phenylene, which is unfused or fused with  $R^{26A}$ ;  $R^{26A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{27}$  is heteroaryl, which is unfused or fused with  $R^{27A}$ ;  $R^{27A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{28}$  is phenylene, which is unfused or fused with  $R^{28A}$ ;  $R^{28A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{29}$  is heteroaryl, which is unfused or fused with  $R^{29A}$ ;  $R^{29A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{30}$  is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with  $R^{30A}$ ;  $R^{30A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{37}$  is a bond or  $R^{37A}$ ;

$R^{37A}$  is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected  $R^{37B}$ ,  $OR^{37B}$ ,  $SR^{37B}$ ,  $S(O)R^{37B}$ ,  $SO_2R^{37B}$ ,  $C(O)R^{37B}$ ,  $CO(O)R^{37B}$ ,  $OC(O)R^{37B}$ ,  $OC(O)OR^{37B}$ ,  $NH_2$ ,  $NHR^{37B}$ ,  $N(R^{37B})_2$ ,  $NHC(O)R^{37B}$ ,  $NR^{37B}C(O)R^{37B}$ ,  $NHS(O)_2R^{37B}$ ,  $NR^{37B}S(O)_2R^{37B}$ ,  $NHC(O)OR^{37B}$ ,  $NR^{37B}C(O)OR^{37B}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{37B}$ ,  $NHC(O)N(R^{37B})_2$ ,  $NR^{37B}C(O)NHR^{37B}$ ,  $NR^{37B}C(O)N(R^{37B})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{37B}$ ,  $C(O)N(R^{37B})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{37B}$ ,  $C(O)NHSO_2R^{37B}$ ,  $C(O)NR^{37B}SO_2R^{37B}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{37B}$ ,  $SO_2N(R^{37B})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{37B}$ ,  $C(N)N(R^{37B})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  and  $T$  substituents;  $R^{37B}$  is alkyl, alkenyl, alkynyl, or  $R^{37C}$ ;

$R^{37C}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

$Z^3$  is  $R^{38}$ ,  $R^{39}$  or  $R^{40}$ ;

$R^{38}$  is phenyl, which is unfused or fused with  $R^{38A}$ ;  $R^{38A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{39}$  is heteroaryl, which is unfused or fused with  $R^{39A}$ ;  $R^{39A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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$R^{40}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{40A}$ ;  $R^{40A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by  $R^{26}$  and  $R^{27}$  are substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are absent) or further substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are present) with  $R^{41}$ ,  $OR^{41}$ ,  $SR^{41}$ ,  $S(O)R^{41}$ ,  $SO_2R^{41}$ ,  $C(O)R^{41}$ ,  $CO(O)R^{41}$ ,  $OC(O)R^{41}$ ,  $OC(O)OR^{41}$ ,  $NHR^{41}$ ,  $N(R^{41})_2$ ,  $NHC(O)R^{41}$ ,  $NR^{41}C(O)R^{41}$ ,  $NHS(O)_2R^{41}$ ,  $NR^{41}S(O)_2R^{41}$ ,  $NHC(O)OR^{41}$ ,  $NR^{41}C(O)OR^{41}$ ,  $NHC(O)NHR^{41}$ ,  $NHC(O)N(R^{41})_2$ ,  $NR^{41}C(O)NHR^{41}$ ,  $NR^{41}C(O)N(R^{41})_2$ ,  $C(O)NHR^{41}$ ,  $C(O)N(R^{41})_2$ ,  $C(O)NHOR^{41}$ ,  $C(O)NHSO_2R^{41}$ ,  $C(O)NR^{41}SO_2R^{41}$ ,  $SO_2NHR^{41}$ ,  $SO_2N(R^{41})_2$ ,  $C(N)NHR^{41}$ , or  $C(N)N(R^{41})_2$ ;

$R^{41}$  is heteroaryl, which is fused with  $R^{43A}$ ;  $R^{43A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused or fused with benzene, heteroarene or  $R^{43B}$ ;  $R^{43B}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by  $E^1$  and  $Y^1$  together,  $Y^1$  and  $B^1$  together,  $A^2$  and  $B^1$  together,  $A^2$  and  $D^1$  together,  $R^{1A}$ ,  $R^2$ ,  $R^{2A}$ ,  $R^3$ ,  $R^{3A}$ ,  $R^4$ ,  $R^{4A}$ ,  $R^6$ ,  $R^{6C}$ ,  $R^8$ ,  $R^{8A}$ ,  $R^9$ ,  $R^{9A}$ ,  $R^{10}$ ,  $R^{10A}$ ,  $R^{13}$ ,  $R^{13A}$ ,  $R^{14}$ ,  $R^{14A}$ ,  $R^{15}$ ,  $R^{15A}$ ,  $R^{18}$ ,  $R^{18A}$ ,  $R^{19}$ ,  $R^{19A}$ ,  $R^{20}$ ,  $R^{20A}$ ,  $R^{23}$ ,  $R^{23A}$ ,  $R^{24}$ ,  $R^{24A}$ ,  $R^{25}$ ,  $R^{25A}$ ,  $R^{26}$ ,  $R^{26A}$ ,  $R^{27}$ ,  $R^{27A}$ ,  $R^{28}$ ,  $R^{28A}$ ,  $R^{29}$ ,  $R^{29A}$ ,  $R^{30}$ ,  $R^{30A}$ ,  $R^{37B}$ ,  $R^{38}$ ,  $R^{38A}$ ,  $R^{39}$ ,  $R^{39A}$ ,  $R^{40}$ , and  $R^{40A}$  are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SR^{57}$ ,  $S(O)R^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $OC(O)OR^{57}$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NR^{57}C(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $NR^{57}S(O)_2R^{57}$ ,  $NHC(O)OR^{57}$ ,  $NR^{57}C(O)OR^{57}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{57}$ ,  $NHC(O)N(R^{57})_2$ ,  $NR^{57}C(O)NHR^{57}$ ,  $NR^{57}C(O)N(R^{57})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{57}$ ,  $C(O)N(R^{57})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{57}$ ,  $C(O)NHSO_2R^{57}$ ,  $C(O)NR^{57}SO_2R^{57}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{57}$ ,  $SO_2N(R^{57})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{57}$ ,  $C(N)N(R^{57})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl, which is unfused or fused with  $R^{58A}$ ;  $R^{58A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{59}$  is heteroaryl, which is unfused or fused with  $R^{59A}$ ;

$R^{59A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{60}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{60A}$ ;  $R^{60A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{61}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $SR^{62}$ ,  $S(O)R^{62}$ ,  $SO_2R^{62}$ ,  $C(O)R^{62}$ ,  $CO(O)R^{62}$ ,  $OC(O)R^{62}$ ,  $OC(O)OR^{62}$ ,  $NH_2$ ,  $NHR^{62}$ ,  $N(R^{62})_2$ ,  $NHC(O)R^{62}$ ,  $NR^{62}C(O)R^{62}$ ,  $NHS(O)_2R^{62}$ ,  $NR^{62}S(O)_2R^{62}$ ,  $NHC(O)OR^{62}$ ,  $NR^{62}C(O)OR^{62}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{62}$ ,  $NHC(O)N(R^{62})_2$ ,  $NR^{62}C(O)NHR^{62}$ ,  $NR^{62}C(O)N(R^{62})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{62}$ ,  $C(O)N(R^{62})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{62}$ ,  $C(O)NHSO_2R^{62}$ ,  $C(O)NR^{62}SO_2R^{62}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{62}$ ,  $SO_2N(R^{62})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{62}$ ,  $C(N)N(R^{62})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{62}$  is  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$  or  $R^{66}$ ;

$R^{63}$  is phenyl, which is unfused or fused with  $R^{63A}$ ;  $R^{63A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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$R^{64}$  is heteroaryl, which is unfused or fused with  $R^{64A}$ ;  $R^{64A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{65}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with  $R^{65A}$ ;  $R^{65A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{66}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{67}$ ,  $OR^{67}$ ,  $SR^{67}$ ,  $S(O)R^{67}$ ,  $SO_2R^{67}$ ,  $C(O)R^{67}$ ,  $CO(O)R^{67}$ ,  $OC(O)R^{67}$ ,  $OC(O)OR^{67}$ ,  $NH_2$ ,  $NHR^{67}$ ,  $N(R^{67})_2$ ,  $NHC(O)R^{67}$ ,  $NR^{67}C(O)R^{67}$ ,  $NHS(O)_2R^{67}$ ,  $NR^{67}S(O)_2R^{67}$ ,  $NHC(O)OR^{67}$ ,  $NR^{67}C(O)OR^{67}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{67}$ ,  $NHC(O)N(R^{67})_2$ ,  $NR^{67}C(O)NHR^{67}$ ,  $NR^{67}C(O)N(R^{67})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{67}$ ,  $C(O)N(R^{67})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{67}$ ,  $C(O)NHSO_2R^{67}$ ,  $C(O)NR^{67}SO_2R^{67}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{67}$ ,  $SO_2N(R^{67})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{67}$ ,  $C(N)N(R^{67})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$  substituents;

$R^{67}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$ ,  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$ , and  $R^{67}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $OR^{68}$ ,  $SR^{68}$ ,  $S(O)R^{68}$ ,  $SO_2R^{68}$ ,  $C(O)R^{68}$ ,  $CO(O)R^{68}$ ,  $OC(O)R^{68}$ ,  $OC(O)OR^{68}$ ,  $NH_2$ ,  $NHR^{68}$ ,  $N(R^{68})_2$ ,  $NHC(O)R^{68}$ ,  $NR^{68}C(O)R^{68}$ ,  $NHS(O)_2R^{68}$ ,  $NR^{68}S(O)_2R^{68}$ ,  $NHC(O)OR^{68}$ ,  $NR^{68}C(O)OR^{68}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{68}$ ,  $NHC(O)N(R^{68})_2$ ,  $NR^{68}C(O)NHR^{68}$ ,  $NR^{68}C(O)N(R^{68})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{68}$ ,  $C(O)N(R^{68})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{68}$ ,  $C(O)NHSO_2R^{68}$ ,  $C(O)NR^{68}SO_2R^{68}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{68}$ ,  $SO_2N(R^{68})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{68}$ ,  $C(N)N(R^{68})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{68}$  is  $R^{69}$ ,  $R^{70}$ ,  $R^{71}$  or  $R^{72}$ ;

$R^{69}$  is phenyl, which is unfused or fused with  $R^{69A}$ ;  $R^{69A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{70}$  is heteroaryl, which is unfused or fused with  $R^{70A}$ ;  $R^{70A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{71}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{71A}$ ;  $R^{71A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{72}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{73}$ ,  $OR^{73}$ ,  $SR^{73}$ ,  $S(O)R^{73}$ ,  $SO_2R^{73}$ ,  $C(O)R^{73}$ ,  $CO(O)R^{73}$ ,  $OC(O)R^{73}$ ,  $OC(O)OR^{73}$ ,  $NH_2$ ,  $NHR^{73}$ ,  $N(R^{73})_2$ ,  $NHC(O)R^{73}$ ,  $NR^{73}C(O)R^{73}$ ,  $NHS(O)_2R^{73}$ ,  $NR^{73}S(O)_2R^{73}$ ,  $NHC(O)OR^{73}$ ,  $NR^{73}C(O)OR^{73}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{73}$ ,  $NHC(O)N(R^{73})_2$ ,  $NR^{73}C(O)NHR^{73}$ ,  $NR^{73}C(O)N(R^{73})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{73}$ ,  $C(O)N(R^{73})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{73}$ ,  $C(O)NHSO_2R^{73}$ ,  $C(O)NR^{73}SO_2R^{73}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{73}$ ,  $SO_2N(R^{73})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{73}$ ,  $C(N)N(R^{73})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

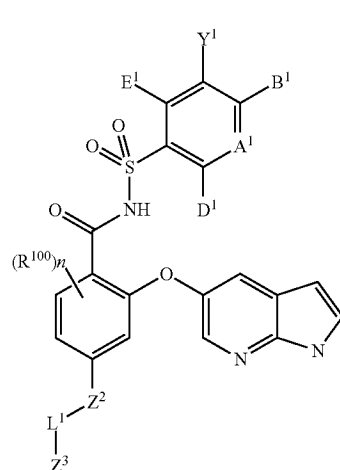
$R^{73}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by  $R^{69}$ ,  $R^{70}$ , and  $R^{71}$  are unsubstituted or substituted with one or two or three or four of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $C(O)NHOH$ ,

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$SO_2NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ .

Another embodiment of this invention pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (II)



(II)

or a therapeutically acceptable salt thereof, wherein

$R^{100}$  is as described for substituents on  $R^{26}$ ;

$n$  is 0, 1, 2, or 3;

$A^1$  is  $N$  or  $C(A^2)$ ;

$A^2$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ;

$B^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ;

$D^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNH_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1A}$ ;

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SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

E<sup>1</sup> is H, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, C(O)OH, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, C(O)R<sup>17</sup>, C(O)OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, NH<sub>2</sub>, NHR<sup>17</sup>, N(R<sup>17</sup>)<sub>2</sub>, NHC(O)R<sup>17</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>17</sup>, C(O)N(R<sup>17</sup>)<sub>2</sub>, NHS(O)R<sup>17</sup> or NHSO<sub>2</sub>R<sup>17</sup>; or

E<sup>1</sup> and Y<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, B<sup>1</sup>, and D<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

A<sup>2</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

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A<sup>2</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

B<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>NHR<sup>1</sup>, NHSO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

R<sup>1</sup> is R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup>;

R<sup>1,4</sup> is cycloalkyl, cycloalkenyl or cycloalkynyl;

R<sup>2</sup> is phenyl, which is unfused or fused with R<sup>2,4</sup>; R<sup>2,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>3</sup> is heteroaryl, which is unfused or fused with R<sup>3,4</sup>; R<sup>3,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>4,4</sup>; R<sup>4,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>5</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>6</sup>, NC(R<sup>6,4</sup>)(R<sup>6,5</sup>), R<sup>7</sup>, OR<sup>7</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, C(O)R<sup>7</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>7</sup>, C(O)N(R<sup>7</sup>)<sub>2</sub>, NHC(O)R<sup>7</sup>, NR<sup>7</sup>C(O)R<sup>7</sup>, NHSO<sub>2</sub>R<sup>7</sup>, NHC(O)OR<sup>7</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>7</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>7</sup>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NHR<sup>7</sup>, OH, (O), C(O)OH, N<sub>3</sub>, CN, NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>6</sup> is C<sub>2</sub>-C<sub>5</sub>-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N<sub>3</sub>, CN, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, NH<sub>2</sub>, NH(CH<sub>3</sub>) or N(CH<sub>3</sub>)<sub>2</sub>;

R<sup>6,4</sup> and R<sup>6,5</sup> are independently selected alkyl or, together with the N to which they are attached, R<sup>6,6</sup>;

R<sup>6,6</sup> is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH<sub>2</sub> moiety unreplaced or replaced with O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup>;

R<sup>8</sup> is phenyl, which is unfused or fused with R<sup>8,4</sup>; R<sup>8,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>9</sup> is heteroaryl, which is unfused or fused with R<sup>9,4</sup>; R<sup>9,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>10,4</sup>; R<sup>10,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>11</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup>, SR<sup>12</sup>, S(O)R<sup>12</sup>, SO<sub>2</sub>R<sup>12</sup>, COR<sup>12</sup>, CO(O)R<sup>12</sup>, OC(O)R<sup>12</sup>, OC(O)OR<sup>12</sup>, NH<sub>2</sub>, NHR<sup>12</sup>, N(R<sup>12</sup>)<sub>2</sub>, NHC(O)R<sup>12</sup>, NR<sup>12</sup>C(O)R<sup>12</sup>, NHS(O)R<sup>12</sup>, NR<sup>12</sup>S(O)R<sup>12</sup>, NHC(O)OR<sup>12</sup>, NR<sup>12</sup>C(O)OR<sup>12</sup>, C(O)OR<sup>12</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>12</sup>, NHC(O)N(R<sup>12</sup>)<sub>2</sub>, NR<sup>12</sup>C(O)NHR<sup>12</sup>, NR<sup>12</sup>C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>12</sup>, C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>12</sup>, C(O)NHSO<sub>2</sub>R<sup>12</sup>, C(O)NHR<sup>12</sup>SO<sub>2</sub>R<sup>12</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>12</sup>, SO<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)



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NH<sub>2</sub>, C(N)NHR<sup>12</sup>, C(N)N(R<sup>12</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>12</sup> is R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> or R<sup>16</sup>;

R<sup>13</sup> is phenyl, which is unfused or fused with R<sup>13A</sup>; R<sup>13A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>14</sup> is heteroaryl, which is unfused or fused with R<sup>14A</sup>; R<sup>14A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>15</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R<sup>15A</sup>; R<sup>15A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>16</sup> is alkyl, alkenyl or alkynyl;

R<sup>17</sup> is R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> or R<sup>21</sup>;

R<sup>18</sup> is phenyl, which is unfused or fused with R<sup>18A</sup>; R<sup>18A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>19</sup> is heteroaryl, which is unfused or fused with R<sup>19A</sup>; R<sup>19A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>20</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R<sup>20A</sup>; R<sup>20A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>21</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, OR<sup>22</sup>, SR<sup>22</sup>, S(O)R<sup>22</sup>, SO<sub>2</sub>R<sup>22</sup>, C(O)R<sup>22</sup>, CO(O)R<sup>22</sup>, OC(O)R<sup>22</sup>, OC(O)OR<sup>22</sup>, NH<sub>2</sub>, NHR<sup>22</sup>, N(R<sup>22</sup>)<sub>2</sub>, NHC(O)R<sup>22</sup>, NR<sup>22</sup>C(O)R<sup>22</sup>, NHS(O)<sub>2</sub>R<sup>22</sup>, NR<sup>22</sup>S(O)<sub>2</sub>R<sup>22</sup>, NHC(O)OR<sup>22</sup>, NR<sup>22</sup>C(O)OR<sup>22</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>22</sup>, NHC(O)N(R<sup>22</sup>)<sub>2</sub>, NR<sup>22</sup>C(O)NHR<sup>22</sup>, NR<sup>22</sup>C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>22</sup>, C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>22</sup>, C(O)NHSO<sub>2</sub>R<sup>22</sup>, C(O)NR<sup>22</sup>SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>22</sup>, SO<sub>2</sub>N(R<sup>22</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>22</sup>, C(N)N(R<sup>22</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>23</sup>, R<sup>24</sup> or R<sup>25</sup>;

R<sup>23</sup> is phenyl, which is unfused or fused with R<sup>23A</sup>; R<sup>23A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>24</sup> is heteroarene, which is unfused or fused with R<sup>24A</sup>; R<sup>24A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>25</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>25A</sup>; R<sup>25A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z<sup>2</sup> is R<sup>28</sup>, R<sup>29</sup> or R<sup>30</sup>;

L<sup>1</sup> is a R<sup>37</sup>, OR<sup>37</sup>, SR<sup>37</sup>, S(O)R<sup>37</sup>, SO<sub>2</sub>R<sup>37</sup>, C(O)R<sup>37</sup>, CO(O)R<sup>37</sup>, OC(O)R<sup>37</sup>, OC(O)OR<sup>37</sup>, NHR<sup>37</sup>, C(O)NH, C(O)NR<sup>37</sup>, C(O)NHOR<sup>37</sup>, C(O)NHSO<sub>2</sub>R<sup>37</sup>, SO<sub>2</sub>NH, SO<sub>2</sub>NHR<sup>37</sup>, C(N)NH, C(N)NHR<sup>37</sup>;

R<sup>28</sup> is phenylene, which is unfused or fused with R<sup>28A</sup>; R<sup>28A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>29</sup> is heteroarylene, which is unfused or fused with R<sup>29A</sup>; R<sup>29A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>30</sup> is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R<sup>30A</sup>; R<sup>30A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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R<sup>37</sup> is a bond or R<sup>37A</sup>;

R<sup>37A</sup> is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R<sup>37B</sup>, OR<sup>37B</sup>, SR<sup>37B</sup>, S(O)R<sup>37B</sup>, SO<sub>2</sub>R<sup>37B</sup>, C(O)R<sup>37B</sup>, CO(O)R<sup>37B</sup>, OC(O)R<sup>37B</sup>, OC(O)OR<sup>37B</sup>, NH<sub>2</sub>, NHR<sup>37B</sup>, N(R<sup>37B</sup>)<sub>2</sub>, NR<sup>37B</sup>C(O)R<sup>37B</sup>, NHS(O)<sub>2</sub>R<sup>37B</sup>, NR<sup>37B</sup>S(O)<sub>2</sub>R<sup>37B</sup>, NHC(O)R<sup>37B</sup>, NR<sup>37B</sup>C(O)OR<sup>37B</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>37B</sup>, NHC(O)N(R<sup>37B</sup>)<sub>2</sub>, NR<sup>37B</sup>C(O)NHR<sup>37B</sup>, NR<sup>37B</sup>C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>37B</sup>, C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>37B</sup>, C(O)NHSO<sub>2</sub>R<sup>37B</sup>, C(O)NR<sup>37B</sup>SO<sub>2</sub>R<sup>37B</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>37B</sup>, SO<sub>2</sub>N(R<sup>37B</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>37B</sup>, C(N)N(R<sup>37B</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br and I substituents;

R<sup>37B</sup> is alkyl, alkenyl, alkynyl, or R<sup>37C</sup>;

R<sup>37C</sup> is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

Z<sup>3</sup> is R<sup>38</sup>, R<sup>39</sup> or R<sup>40</sup>;

R<sup>38</sup> is phenyl, which is unfused or fused with R<sup>38A</sup>; R<sup>38A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>39</sup> is heteroaryl, which is unfused or fused with R<sup>39A</sup>; R<sup>39A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>40</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>40A</sup>; R<sup>40A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by E<sup>1</sup> and Y<sup>1</sup> together, Y<sup>1</sup> and B<sup>1</sup> together, A<sup>2</sup> and B<sup>1</sup> together, A<sup>2</sup> and D<sup>1</sup> together, R<sup>1A</sup>, R<sup>2</sup>, R<sup>2A</sup>, R<sup>3</sup>, R<sup>3A</sup>, R<sup>4</sup>, R<sup>4A</sup>, R<sup>6</sup>, R<sup>6C</sup>, R<sup>8</sup>, R<sup>8A</sup>, R<sup>9</sup>, R<sup>9A</sup>, R<sup>10</sup>, R<sup>10A</sup>, R<sup>13</sup>, R<sup>13A</sup>, R<sup>14</sup>, R<sup>14A</sup>, R<sup>15</sup>, R<sup>15A</sup>, R<sup>18</sup>, R<sup>18A</sup>, R<sup>19</sup>, R<sup>19A</sup>, R<sup>20</sup>, R<sup>20A</sup>, R<sup>23</sup>, R<sup>23A</sup>, R<sup>24</sup>, R<sup>24A</sup>, R<sup>25</sup>, R<sup>25A</sup>, R<sup>26</sup>, R<sup>26A</sup>, R<sup>27</sup>, R<sup>27A</sup>, R<sup>28</sup>, R<sup>28A</sup>, R<sup>29</sup>, R<sup>29A</sup>, R<sup>30</sup>, R<sup>30A</sup>, R<sup>37B</sup>, R<sup>38</sup>, R<sup>38A</sup>, R<sup>39</sup>, R<sup>39A</sup>, R<sup>40</sup>, and R<sup>40A</sup> are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SR<sup>57</sup>, S(O)R<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, OC(O)R<sup>57</sup>, OC(O)OR<sup>57</sup>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NR<sup>57</sup>C(O)R<sup>57</sup>, NHS(O)<sub>2</sub>R<sup>57</sup>, NR<sup>57</sup>S(O)<sub>2</sub>R<sup>57</sup>, NHC(O)OR<sup>57</sup>, NR<sup>57</sup>C(O)OR<sup>57</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>57</sup>, NHC(O)N(R<sup>57</sup>)<sub>2</sub>, NR<sup>57</sup>C(O)NHR<sup>57</sup>, NR<sup>57</sup>C(O)N(R<sup>57</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>57</sup>, C(O)NHSO<sub>2</sub>R<sup>57</sup>, C(O)NR<sup>57</sup>SO<sub>2</sub>R<sup>57</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>57</sup>, SO<sub>2</sub>N(R<sup>57</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>57</sup>, C(N)N(R<sup>57</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>57A</sup> is spiroalkyl or heterospiroalkyl;

R<sup>57</sup> is R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup> or R<sup>61</sup>;

R<sup>58</sup> is phenyl, which is unfused or fused with R<sup>58A</sup>; R<sup>58A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>59</sup> is heteroaryl, which is unfused or fused with R<sup>59A</sup>; R<sup>59A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>60</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>60A</sup>; R<sup>60A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>61</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, SR<sup>62</sup>, S(O)R<sup>62</sup>, SO<sub>2</sub>R<sup>62</sup>, C(O)R<sup>62</sup>, CO(O)R<sup>62</sup>, OC(O)R<sup>62</sup>, OC(O)OR<sup>62</sup>, NH<sub>2</sub>, NHR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, NHC(O)R<sup>62</sup>, NR<sup>62</sup>C(O)R<sup>62</sup>, NHS(O)<sub>2</sub>R<sup>62</sup>, NR<sup>62</sup>S(O)<sub>2</sub>R<sup>62</sup>, NHC(O)OR<sup>62</sup>, NR<sup>62</sup>C(O)OR<sup>62</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>62</sup>, NHC(O)N(R<sup>62</sup>)<sub>2</sub>, NR<sup>62</sup>C(O)NHR<sup>62</sup>, NR<sup>62</sup>C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>62</sup>, C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>62</sup>, C(O)NHSO<sub>2</sub>R<sup>62</sup>, C(O)NR<sup>62</sup>SO<sub>2</sub>R<sup>62</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>62</sup>, SO<sub>2</sub>N(R<sup>62</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>62</sup>, C(N)N(R<sup>62</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I substituents;



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(R<sup>62</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>62</sup>, C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>62</sup>, C(O)NHSO<sub>2</sub>R<sup>62</sup>, C(O)NR<sup>62</sup>SO<sub>2</sub>R<sup>62</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>62</sup>, SO<sub>2</sub>N(R<sup>62</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>62</sup>, C(N)N(R<sup>62</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>62</sup> is R<sup>63</sup>, R<sup>64</sup>, R<sup>65</sup> or R<sup>66</sup>;

R<sup>63</sup> is phenyl, which is unfused or fused with R<sup>63,4</sup>; R<sup>63,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>64</sup> is heteroaryl, which is unfused or fused with R<sup>64,4</sup>; R<sup>64,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>65</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>65,4</sup>; R<sup>65,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>66</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>67</sup>, OR<sup>67</sup>, SR<sup>67</sup>, S(O)R<sup>67</sup>, SO<sub>2</sub>R<sup>67</sup>, C(O)R<sup>67</sup>, CO(O)R<sup>67</sup>, OC(O)R<sup>67</sup>, OC(O)OR<sup>67</sup>, NH<sub>2</sub>, NHR<sup>67</sup>, N(R<sup>67</sup>)<sub>2</sub>, NHC(O)R<sup>67</sup>, NR<sup>67</sup>C(O)R<sup>67</sup>, NHS(O)<sub>2</sub>R<sup>67</sup>, NR<sup>67</sup>S(O)<sub>2</sub>R<sup>67</sup>, NHC(O)OR<sup>67</sup>, NR<sup>67</sup>C(O)OR<sup>67</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>67</sup>, NHC(O)N(R<sup>67</sup>)<sub>2</sub>, NR<sup>67</sup>C(O)NHR<sup>67</sup>, NR<sup>67</sup>C(O)N(R<sup>67</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>67</sup>, C(O)N(R<sup>67</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>67</sup>, C(O)NHSO<sub>2</sub>R<sup>67</sup>, C(O)NR<sup>67</sup>SO<sub>2</sub>R<sup>67</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>67</sup>, SON(R<sup>67</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>67</sup>, C(N)N(R<sup>67</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I substituents;

R<sup>67</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R<sup>57,4</sup>, R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup>, R<sup>63</sup>, R<sup>64</sup>, R<sup>65</sup>, and R<sup>67</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, OR<sup>68</sup>, SR<sup>68</sup>, S(O)R<sup>68</sup>, SO<sub>2</sub>R<sup>68</sup>, C(O)R<sup>68</sup>, CO(O)R<sup>68</sup>, OC(O)R<sup>68</sup>, OC(O)OR<sup>68</sup>, NH<sub>2</sub>, NHR<sup>68</sup>, N(R<sup>68</sup>)<sub>2</sub>, NHC(O)R<sup>68</sup>, NR<sup>68</sup>C(O)R<sup>68</sup>, NHS(O)<sub>2</sub>R<sup>68</sup>, NR<sup>68</sup>S(O)<sub>2</sub>R<sup>68</sup>, NHC(O)OR<sup>68</sup>, NR<sup>68</sup>C(O)OR<sup>68</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>68</sup>, NHC(O)N(R<sup>68</sup>)<sub>2</sub>, NR<sup>68</sup>C(O)NHR<sup>68</sup>, NR<sup>68</sup>C(O)N(R<sup>68</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>68</sup>, C(O)N(R<sup>68</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>68</sup>, C(O)NHSO<sub>2</sub>R<sup>68</sup>, C(O)NR<sup>68</sup>SO<sub>2</sub>R<sup>68</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>68</sup>, SO<sub>2</sub>N(R<sup>68</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>68</sup>, C(N)N(R<sup>68</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>68</sup> is R<sup>69</sup>, R<sup>70</sup>, R<sup>71</sup> or R<sup>72</sup>;

R<sup>69</sup> is phenyl, which is unfused or fused with R<sup>69,4</sup>; R<sup>69,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>70</sup> is heteroaryl, which is unfused or fused with R<sup>70,4</sup>; R<sup>70,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>71</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>71,4</sup>; R<sup>71,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>72</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>73</sup>, OR<sup>73</sup>, SR<sup>73</sup>, S(O)R<sup>73</sup>, SO<sub>2</sub>R<sup>73</sup>, C(O)R<sup>73</sup>, CO(O)R<sup>73</sup>, OC(O)R<sup>73</sup>, OC(O)OR<sup>73</sup>, NH<sub>2</sub>, NHR<sup>73</sup>, N(R<sup>73</sup>)<sub>2</sub>, NHC(O)R<sup>73</sup>, NR<sup>73</sup>C(O)R<sup>73</sup>, NHS(O)<sub>2</sub>R<sup>73</sup>, NR<sup>73</sup>S(O)<sub>2</sub>R<sup>73</sup>, NHC(O)OR<sup>73</sup>, NR<sup>73</sup>C(O)OR<sup>73</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>73</sup>, NHC(O)N(R<sup>73</sup>)<sub>2</sub>, NR<sup>73</sup>C(O)NHR<sup>73</sup>, NR<sup>73</sup>C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>73</sup>, C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>73</sup>, C(O)NHSO<sub>2</sub>R<sup>73</sup>, C(O)NR<sup>73</sup>SO<sub>2</sub>R<sup>73</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>73</sup>, SO<sub>2</sub>N(R<sup>73</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>73</sup>, C(N)N(R<sup>73</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

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NH<sub>2</sub>, C(N)NHR<sup>73</sup>, C(N)N(R<sup>73</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>73</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R<sup>69</sup>, R<sup>70</sup>, and R<sup>71</sup> are unsubstituted or substituted with one or two or three or four of independently selected NH<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H, and G<sup>1</sup> is H.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; G<sup>1</sup> is H, and B<sup>1</sup> is NHR<sup>1</sup>.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; G<sup>1</sup> is H, B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; G<sup>1</sup> is H, B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

Another embodiment pertains to compounds of Formula (I) wherein A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; G<sup>1</sup> is H, B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylpiperidin-4-yl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(1,4-dioxan-2-yl-methoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{(tetrahydro-2H-pyran-4-ylmethyl)amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-ylmethoxy)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)amino]-3-(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5-[(4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;

N-[(5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2,2-dimethyltetrahydro-

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2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({4-[(1-acetyl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethoxy)ethyl]sulfonyl)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-N-({[4-({4-bis(cyclopropylmethyl)amino)cyclohexyl]amino)-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 tert-butyl 3-({4-({4-({[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxymethyl)morpholine-4-carboxylate;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylsulfonyl)piperidin-4-yl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({4-chloro-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-



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2H-pyran-4-ylpiperidin-4-yl)oxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 and therapeutically acceptable salts, and metabolites thereof.  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-(2,2-difluoroethyl)piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1-(1-cyclopropylpiperidin-4-yl)amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-yl)-N-{[4-({1-(1-morpholin-4-ylcyclohexyl)methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-(dicyclopropylamino)cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-(ethylmorpholin-3-yl)methoxy]pyridin-3-yl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({1,1-dioxidothiomorpholin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-{[4-({[4-aminotetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1S,3R]-3-morpholin-4-ylcyclopentyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1R,3S]-3-morpholin-4-ylcyclopentyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[morpholin-2-ylmethyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 40 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 45 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;  
 50 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;  
 55 Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({4-(cyclopropylamino)cyclohexyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 60 Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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Trans-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-{{[4-({[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl]-4-fluoropiperidine-1-carboxylate;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cyclohexyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1-2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclobutylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-{{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(1-acetyl)piperidin-3-yl]methyl}amino}-3-nitrophenyl)sulfonyl]-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[1-2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-{{[1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-{{[1-2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}methyl}amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(1-cyclopropyl)piperidin-4-yl]methyl}amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-{{[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-{{[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-[[4-(fluoro-1-oxetan-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(4-cyclobutyl)morpholin-3-yl]methyl}amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(4-tetrahydrofuran-3-yl)morpholin-3-yl]methyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-{{[1-2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}methyl}amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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ethyl)ethyl]piperidin-4-yl] methylamino]-3-nitrophenyl] sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-({4-[(4-methoxybenzyl) amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-({4-[(3-methoxybenzyl) amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(4-{[4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(4-{[4-(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl]sulfonyl}]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-({4-[(4-hydroxybenzyl) amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-({4-[(3-hydroxybenzyl) amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(4-{[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl] methyl} piperazin-1-yl)-N-[(4-{[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(2-morpholin-4-ylethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

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droxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(2-methoxyethoxy)ethyl]morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

(2-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl}amino)methyl)morpholin-4-yl]acetic acid;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-



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pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

ethyl 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-{[(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl}amino]piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro- $\lambda^6$ -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-{(3R)-tetrahydrofuran-3-ylamino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(1,3-difluoropropan-



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2-yl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[3-nitro-4-[[1-(oxetan-3-yl)azetidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((2R)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((2S)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-(cyanomethyl)pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 N-((5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 10 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-((5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 20 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-((4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)-3-(trifluoromethyl)phenyl)sulfonyl)benzamide;  
 25 N-[(5-chloro-6-[[1-(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(trans-4-cyanocyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((4-[(trans-4-cyanocyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 40 N-[(5-chloro-6-[[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 45 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-(3-furylmethoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 50 N-[(5-chloro-6-[[1-(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 55 N-[(5-chloro-6-[[1-(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 60 N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 65 N-((3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-

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dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-([1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-([1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropylamino)propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(methoxyacetyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)benzamide;  
 N-([5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-[(4-fluorotetrahy-

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dro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([trans-4-(morpholin-4-yl)cyclohexyl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(2,2,2-trifluoroethyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(oxetan-3-yl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(oxetan-3-yl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([2S)-4-cyclopropylmorpholin-2-yl]methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-

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pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 methyl 2-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]methyl]morpholine-4-carboxylate;

10 2-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3-cyclobutyl(cyclopropyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(trans-4-hydroxycyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

40 N-{[3-chloro-4-{[4-fluorotetrahydro-2H-pyran-4-yl]methoxy}phenyl]sulfonyl}-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

45 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

50 4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{[4-cyclopropyl(oxetan-3-yl)amino]cyclohexyl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-{[4-[(4-cyclopropylmorpholin-2-yl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

65 N-{[3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimeth-

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ylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-{[4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 2-{[(2-chloro-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

10 (2S)-2-{[(3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

15 N-{[5-chloro-6-{[4-cyclopropylmorpholin-2-yl)methyl]amino}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 2-{[(3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

35 N-{[5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

40 N-{[5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl]sulfonyl}-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

50 N-{[5-chloro-6-{[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

55 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

60 N-{[5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

65 (1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

{4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)amino)methyl pivalate;

{4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)amino)methyl butyrate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl)-2-nitrophenyl)morpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(methoxymethyl)cyclohexyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[(1-(1,3-thiazol-2-yl)piperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-py-



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ran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-[(5-chloro-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-py-

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ran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(5-chloro-6-[(1-cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[(1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-[(5-chloro-6-[(1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-

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pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to a composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of a compound of Formula (I) or Formula (II).

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or Formula (II).

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said method comprising administering to the patient therapeutically effective amount of the compound of Formula (I) or Formula (II) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

#### DETAILED DESCRIPTION OF THE INVENTION

Variable moieties herein are represented by identifiers (capital letters with numerical and/or alphabetical superscripts) and may be specifically embodied.

It is meant to be understood that proper valences are maintained for all moieties and combinations thereof, that monovalent moieties having more than one atom are drawn from left to right and are attached through their left ends, and that divalent moieties are also drawn from left to right.

It is also meant to be understood that a specific embodiment of a variable moiety herein may be the same or different as another specific embodiment having the same identifier.

The term "alkenyl" as used herein, means a straight or branched hydrocarbon chain containing from 2 to 10 carbons and containing at least one carbon-carbon double bond. The term "C<sub>x</sub>-C<sub>y</sub> alkenyl" means a straight or branched hydrocarbon chain containing at least one carbon-carbon double bond containing x to y carbon atoms. The term "C<sub>3</sub>-C<sub>6</sub> alkenyl" means an alkenyl group containing 3-6 carbon atoms. Representative examples of alkenyl include, but are not limited to, buta-2,3-dienyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

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The term “alkenylene” means a divalent group derived from a straight or branched chain hydrocarbon of 2 to 4 carbon atoms and contains at least one carbon-carbon double bond. The term “C<sub>x</sub>-C<sub>y</sub> alkenylene” means a divalent group derived from a straight or branched hydrocarbon chain containing at least one carbon-carbon double bond and containing x to y carbon atoms. Representative examples of alkenylene include, but are not limited to, —CH=CH— and —CH<sub>2</sub>CH=CH—.

The term “alkyl” as used herein, means a straight or branched, saturated hydrocarbon chain containing from 1 to 10 carbon atoms. The term “C<sub>x</sub>-C<sub>y</sub> alkyl” means a straight or branched chain, saturated hydrocarbon containing x to y carbon atoms. For example “C<sub>1</sub>-C<sub>6</sub> alkyl” means a straight or branched chain, saturated hydrocarbon containing 2 to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term “alkylene” means a divalent group derived from a straight or branched, saturated hydrocarbon chain of 1 to 10 carbon atoms, for example, of 1 to 4 carbon atoms. The term “C<sub>x</sub>-C<sub>y</sub> alkylene” means a divalent group derived from a straight or branched chain, saturated hydrocarbon containing x to y carbon atoms. For example “C<sub>2</sub>-C<sub>6</sub> alkylene” means a straight or branched chain, saturated hydrocarbon containing 2 to 6 carbon atoms. Representative examples of alkylene include, but are not limited to, —CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>—, and —CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>—.

The term “alkynyl” as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. The term “C<sub>x</sub>-C<sub>y</sub> alkynyl” means a straight or branched chain hydrocarbon group containing from x to y carbon atoms. For example “C<sub>3</sub>-C<sub>6</sub> alkynyl” means a straight or branched chain hydrocarbon group containing from 3 to 6 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited to, acetylenyl, 1-propynyl, 2-propynyl, 3-butylnyl, 2-pentylnyl, and 1-butylnyl.

The term “alkynylene,” as used herein, means a divalent radical derived from a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond.

The term “aryl” as used herein, means phenyl.

The term “cyclic moiety,” as used herein, means benzene, phenyl, phenylene, cycloalkane, cycloalkyl, cycloalkylene, cycloalkene, cycloalkenyl, cycloalkenylene, cycloalkyne, cycloalkynyl, cycloalkynylene, heteroarene, heteroaryl, heterocycloalkane, heterocycloalkyl, heterocycloalkene, heterocycloalkenyl and spiroalkyl.

The term “cycloalkylene” or cycloalkyl” or “cycloalkane” as used herein, means a monocyclic or bridged hydrocarbon ring system. The monocyclic cycloalkyl is a carbocyclic ring system containing three to ten carbon atoms, zero heteroatoms and zero double bonds. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The monocyclic ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. Representative examples of such bridged cycloalkyl ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[4.2.1]nonane, tricyclo[3.3.1.0<sup>3,7</sup>]nonane

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(octahydro-2,5-methanopentalene or noradamantane), and tricyclo[3.3.1.1<sup>3,7</sup>]decane (adamantane). The monocyclic and bridged cycloalkyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring system.

The term “cycloalkenylene,” or “cycloalkenyl” or “cycloalkene” as used herein, means a monocyclic or a bridged hydrocarbon ring system. The monocyclic cycloalkenyl has four to ten carbon atoms and zero heteroatoms. The four-membered ring systems have one double bond, the five- or six-membered ring systems have one or two double bonds, the seven- or eight-membered ring systems have one, two, or three double bonds, and the nine- or ten-membered rings have one, two, three, or four double bonds. Representative examples of monocyclic cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. The monocyclic cycloalkenyl ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. Representative examples of the bridged cycloalkenyl groups include, but are not limited to, 4,5,6,7-tetrahydro-3aH-indene, octahydronaphthalenyl, and 1,6-dihydro-pentalene. The monocyclic and bridged cycloalkenyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems.

The term “cycloalkyne,” or “cycloalkynyl,” or “cycloalkynylene,” as used herein, means a monocyclic or a bridged hydrocarbon ring system. The monocyclic cycloalkynyl has eight or more carbon atoms, zero heteroatoms, and one or more triple bonds. The monocyclic cycloalkynyl ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. The monocyclic and bridged cycloalkynyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems.

The term “heteroarene,” or “heteroaryl,” or “heteroarylene,” as used herein, means a five-membered or six-membered aromatic ring having at least one carbon atom and one or more than one independently selected nitrogen, oxygen or sulfur atom. The heteroarenes of this invention are connected through any adjacent atoms in the ring, provided that proper valences are maintained. Representative examples of heteroaryl include, but are not limited to, furanyl (including, but not limited thereto, furan-2-yl), imidazolyl (including, but not limited thereto, 1H-imidazol-1-yl), isoxazolyl, isothiazolyl, oxadiazolyl, 1,3-oxazolyl, pyridinyl (e.g. pyridin-4-yl, pyridin-2-yl, pyridin-3-yl), pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, 1,3-thiazolyl, thienyl (including, but not limited thereto, thien-2-yl, thien-3-yl), triazolyl, and triazinyl.

The term “heterocycloalkane,” or “heterocycloalkyl,” or “heterocycloalkylene,” as used herein, means monocyclic or bridged three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S and zero double bonds. The monocyclic and bridged heterocycloalkane are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the rings. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be oxidized and the nitrogen atoms may optionally be quarternized. Representative examples of heterocycloalkane groups include, but are not limited to, morpholinyl, tetrahydropyran-yl, pyrrolidinyl, piperidinyl, dioxolanyl, tetrahydrofuran-yl, thiomorpholinyl, 1,4-dioxanyl, tetrahydrothienyl, tetrahy-



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drothiopyranyl, oxetanyl, piperazinyl, imidazolidinyl, azetidine, azepanyl, aziridinyl, diazepanyl, dithiolanyl, dithianyl, isoxazolidinyl, isothiazolidinyl, oxadiazolidinyl, oxazolidinyl, pyrazolidinyl, tetrahydrothienyl, thiadiazolidinyl, thiazolidinyl, thiomorpholinyl, trithianyl, and trithianyl.

The term "heterocycloalkene," or "heterocycloalkenyl," or "heterocycloalkenylene," as used herein, means monocyclic or bridged three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S and one or more double bonds. The monocyclic and bridged heterocycloalkene are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the rings. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be oxidized and the nitrogen atoms may optionally be quarternized. Representative examples of heterocycloalkene groups include, but are not limited to, 1,4,5,6-tetrahydropyridazinyl, 1,2,3,6-tetrahydropyridinyl, dihydropyranal, imidazolinyl, isothiazolinyl, oxadiazolinyl, isoxazolinyl, oxazolinyl, pyranal, pyrazolinyl, pyrrolinyl, thiadiazolinyl, thiazolinyl, and thiopyranal.

The term "phenyl," as used herein, means a monovalent radical formed by removal of a hydrogen atom from benzene.

The term "phenylene," as used herein, means a divalent radical formed by removal of a hydrogen atom from phenyl.

The term "spiroalkyl," as used herein, means alkylene, both ends of which are attached to the same carbon atom and is exemplified by C<sub>2</sub>-spiroalkyl, C<sub>3</sub>-spiroalkyl, C<sub>4</sub>-spiroalkyl, C<sub>5</sub>-spiroalkyl, C<sub>6</sub>-spiroalkyl, C<sub>7</sub>-spiroalkyl, C<sub>8</sub>-spiroalkyl, C<sub>9</sub>-spiroalkyl and the like.

The term "spiroheteroalkyl," as used herein, means spiroalkyl having one or two CH<sub>2</sub> moieties replaced with independently selected O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties unreplaced or replaced with N.

The term "spiroheteroalkenyl," as used herein, means spiroalkenyl having one or two CH<sub>2</sub> moieties replaced with independently selected O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties unreplaced or replaced with N and also means spiroalkenyl having one or two CH<sub>2</sub> moieties unreplaced or replaced with independently selected O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties replaced with N.

The term "C<sub>2</sub>-C<sub>5</sub>-spiroalkyl," as used herein, means C<sub>2</sub>-spiroalkyl, C<sub>3</sub>-spiroalkyl, C<sub>4</sub>-spiroalkyl, and C<sub>5</sub>-spiroalkyl.

The term "C<sub>2</sub>-spiroalkyl," as used herein, means eth-1,2-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term "C<sub>3</sub>-spiroalkyl," as used herein, means prop-1,3-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term "C<sub>4</sub>-spiroalkyl," as used herein, means but-1,4-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term "C<sub>5</sub>-spiroalkyl," as used herein, means pent-1,5-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term "C<sub>6</sub>-spiroalkyl," as used herein, means hex-1,6-ylene, both ends of which replace hydrogen atoms of the same CH<sub>2</sub> moiety.

The term "NH protecting group," as used herein, means trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, para-nitrobenzylcarbonyl, ortho-bromobenzyloxycarbonyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, phenyl acetyl, formyl, acetyl, benzoyl, tert-amylloxycarbonyl, tert-butoxycarbonyl, para-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyl-oxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 2-furfuryl-oxycarbonyl,

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diphenylmethoxycarbonyl, 1,1-dimethylpropoxy-carbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantylloxycarbonyl, 8-quinolyloxycarbonyl, benzyl, diphenylmethyl, triphenylmethyl, 2-nitrophenylthio, methanesulfonyl, para-toluenesulfonyl, N,N-dimethylaminomethylene, benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthyl-methylene, 3-hydroxy-4-pyridylmethylene, cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxocyclohexylidene, diphenylphosphoryl, dibenzylphosphoryl, 5-methyl-2-oxo-2H-1,3-dioxol-4-yl-methyl, trimethylsilyl, triethylsilyl, and triphenylsilyl.

The term "C(O)OH protecting group," as used herein, means methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, tert-butyl, phenyl, naphthyl, benzyl, diphenylmethyl, triphenylmethyl, para-nitrobenzyl, para-methoxybenzyl, bis(para-methoxyphenyl)methyl, acetylmethyl, benzoylmethyl, para-nitrobenzoylmethyl, para-bromobenzoylmethyl, para-methanesulfonylbenzoylmethyl, 2-tetrahydropyranal 2-tetrahydrofuranal, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, phthalimidomethyl, succinimidomethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, methylthiomethyl, 2-methylthioethyl, phenylthiomethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyl dimethylsilyl, tert-butyl diphenylsilyl, diphenylmethylsilyl, and tert-butyl methoxyphenylsilyl.

The term "OH or SH protecting group," as used herein, means benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantylloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, S-benzylthiocarbonyl, 4-ethoxy-1-naphthylloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxycetyl, pivaloyl, benzoyl, methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl(phenylmethyl), para-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, tetrahydrofuryl, tetrahydropyranal, tetrahydrothiopyranal, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyl dimethylsilyl, tert-butyl diphenylsilyl, diphenylmethylsilyl, and tert-butyl methoxyphenylsilyl.

Compounds

Geometric isomers may exist in the present compounds. Compounds of this invention may contain carbon-carbon double bonds or carbon-nitrogen double bonds in the E or Z configuration, wherein the term "E" represents higher order substituents on opposite sides of the carbon-carbon or carbon-nitrogen double bond and the term "Z" represents higher order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond as determined by the Cahn-Ingold-Prelog Priority Rules. The compounds of this invention may also exist as a mixture of "E" and "Z" isomers. Substituents around a cycloalkyl or heterocycloalkyl are designated as being of cis or trans configuration. Furthermore,



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the invention contemplates the various isomers and mixtures thereof resulting from the disposal of substituents around an adamantane ring system. Two substituents around a single ring within an adamantane ring system are designated as being of Z or E relative configuration. For examples, see C. D. Jones, M. Kaselj, R. N. Salvatore, W. J. le Noble *J. Org. Chem.* 1998, 63, 2758-2760.

Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms "R" and "S" are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

#### Isotope Enriched or Labeled Compounds

Compounds of the invention can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to,  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ ,  $^{36}\text{Cl}$ , and  $^{125}\text{I}$ . Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

In another embodiment, the isotope-labeled compounds contain deuterium ( $^2\text{H}$ ), tritium ( $^3\text{H}$ ) or  $^{14}\text{C}$  isotopes. Isotope-labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotope-labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples disclosed herein and Schemes by substituting a readily available isotope-labeled reagent for a non-labeled reagent. In some instances, compounds may be treated with isotope-labeled reagents to exchange a normal atom with its isotope, for example, hydrogen for deuterium can be exchanged by the action of a deuterium acid such as  $\text{D}_2\text{SO}_4/\text{D}_2\text{O}$ . In addition to the above, relevant procedures and intermediates are disclosed, for instance, in Lizondo, J et al., *Drugs Fut*, 21(11), 1116 (1996); Brickner, S J et al., *J Med Chem*, 39(3), 673 (1996); Mallesham, B et al., *Org Lett*, 5(7), 963 (2003); PCT publications WO1997010223, WO2005099353, WO1995007271, WO2006008754; U.S. Pat. Nos. 7,538,189; 7,534,814; 7,531,685; 7,528,131; 7,521,421; 7,514,068; 7,511,013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; and 20090082471, the methods are hereby incorporated by reference.

The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of Bcl-2 inhibitors in binding assays. Isotope containing compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the nonisotope-labeled parent compound (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., *Advances in Drug Research Vol. 14*, pp. 2-36, Academic press, London,

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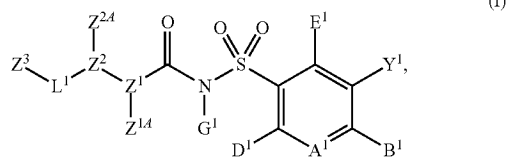
1985; Kato et al., *J. Labelled Comp. Radiopharmaceut.*, 36(10):927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999).

In addition, non-radio active isotope containing drugs, such as deuterated drugs called "heavy drugs," can be used for the treatment of diseases and conditions related to Bcl-2 activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %. Replacement of up to about 15% of normal atom with a heavy isotope has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, *Ann. N.Y. Acad. Sci.* 1960 84: 770; Thomson J F, *Ann. New York Acad. Sci.* 1960 84: 736; Czajka D M et al., *Am. J. Physiol.* 1961 201: 357). Acute replacement of as high as 15%-23% in human fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp. 125-134; *Diabetes Metab.* 23: 251 (1997)).

Stable isotope labeling of a drug can alter its physicochemical properties such as pKa and lipid solubility. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. Accordingly, the incorporation of an isotope at a site of metabolism or enzymatic transformation will slow said reactions potentially altering the pharmacokinetic profile or efficacy relative to the non-isotopic compound.

Suitable groups for  $\text{A}^1$ ,  $\text{B}^1$ ,  $\text{D}^1$ ,  $\text{E}^1$ ,  $\text{G}^1$ ,  $\text{Y}^1$ ,  $\text{L}^1$ ,  $\text{Z}^{1,4}$ ,  $\text{Z}^{2,4}$ ,  $\text{Z}^1$ ,  $\text{Z}^2$ , and  $\text{Z}^3$  in compounds of Formula (I) are independently selected. The described embodiments of the present invention may be combined. Such combination is contemplated and within the scope of the present invention. For example, it is contemplated that embodiments for any of  $\text{A}^1$ ,  $\text{B}^1$ ,  $\text{D}^1$ ,  $\text{E}^1$ ,  $\text{G}^1$ ,  $\text{Y}^1$ ,  $\text{L}^1$ ,  $\text{Z}^{1,4}$ ,  $\text{Z}^{2,4}$ ,  $\text{Z}^1$ ,  $\text{Z}^2$ ,  $\text{L}$  and  $\text{Z}^3$  can be combined with embodiments defined for any other of  $\text{A}^1$ ,  $\text{B}^1$ ,  $\text{D}^1$ ,  $\text{E}^1$ ,  $\text{G}^1$ ,  $\text{Y}^1$ ,  $\text{L}^1$ ,  $\text{Z}^{1,4}$ ,  $\text{Z}^{2,4}$ ,  $\text{Z}^1$ ,  $\text{Z}^2$ , and  $\text{Z}^3$ .

One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins, the compounds having Formula (I)



wherein

$\text{A}^1$  is N or C( $\text{A}^2$ );

$\text{A}^2$  is H,  $\text{R}^1$ ,  $\text{OR}^1$ ,  $\text{SR}^1$ ,  $\text{S}(\text{O})\text{R}^1$ ,  $\text{SO}_2\text{R}^1$ ,  $\text{C}(\text{O})\text{R}^1$ ,  $\text{OC}(\text{O})\text{R}^1$ ,  $\text{NHR}^1$ ,  $\text{N}(\text{R}^1)_2$ ,  $\text{C}(\text{O})\text{NHR}^1$ ,  $\text{C}(\text{O})\text{N}(\text{R}^1)_2$ ,  $\text{NHC}(\text{O})\text{R}^1$ ,  $\text{NR}^1\text{C}(\text{O})\text{R}^1$ ,  $\text{NHC}(\text{O})\text{OR}^1$ ,  $\text{NR}^1\text{C}(\text{O})\text{OR}^1$ ,  $\text{NHC}(\text{O})\text{NH}_2$ ,  $\text{NHC}(\text{O})\text{NHR}^1$ ,  $\text{NHC}(\text{O})\text{N}(\text{R}^1)_2$ ,  $\text{NR}^1\text{C}(\text{O})\text{NHR}^1$ ,  $\text{NR}^1\text{C}(\text{O})$

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$N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHOH$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$B^1$  is H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHOH$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$D^1$  is H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHOH$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$E^1$  is H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHOH$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; and

$Y^1$  is H, CN,  $NO_2$ ,  $C(O)OH$ , F, Cl, Br, I,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ ,  $OCF_2CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $C(O)R^{17}$ ,  $C(O)OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ ,  $NH_2$ ,  $NHR^{17}$ ,  $N(R^{17})_2$ ,  $NHC(O)R^{17}$ ,  $C(O)NH_2$ ,  $C(O)NHR^{17}$ ,  $C(O)N(R^{17})_2$ ,  $NHS(O)R^{17}$  or  $NHSO_2R^{17}$ ; or

$E^1$  and  $Y^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$A^2$ ,  $B^1$ , and  $D^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHOH$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

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$A^2$ ,  $D^1$ , and  $E^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHOH$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$A^2$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$D^1$ ,  $E^1$ , and  $Y^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHOH$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$A^2$  and  $D^1$ , together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$B^1$ ,  $E^1$ , and  $Y^1$  are independently selected H,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHOH$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ , F, Cl, Br, I, CN,  $NO_2$ ,  $N_3$ , OH,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$G^1$  is H, or  $C(O)OR$ ;

R is alkyl;

$R^1$  is  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$ ;

$R^{1,4}$  is cycloalkyl, cycloalkenyl or cycloalkynyl;

$R^2$  is phenyl, which is unfused or fused with  $R^{2,4}$ ;  $R^{2,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^3$  is heteroaryl, which is unfused or fused with  $R^{3,4}$ ;  $R^{3,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^4$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{4,4}$ ;  $R^{4,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^5$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^6$ ,  $NC(R^{6A})(R^{6B})$ ,  $R^7$ ,  $OR^7$ ,  $SR^1$ ,  $S(O)R^7$ ,  $SO_2R^7$ ,  $NHR^7$ ,  $N(R^7)_2$ ,  $C(O)R^7$ ,  $C(O)NH_2$ ,  $C(O)NHR^7$ ,  $C(O)N(R^7)_2$ ,  $NHC(O)R^7$ ,  $NR^7C(O)R^7$ ,  $NHSO_2R^7$ ,  $NHC(O)OR^7$ ,  $SO_2NH_2$ ,  $SO_2NHR^7$ ,  $SO_2N(R^7)_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^7$ ,  $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$ ,  $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^7$ , OH, (O),  $C(O)OH$ ,  $N_3$ , CN,  $NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

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R<sup>6</sup> is C<sub>2</sub>-C<sub>5</sub>-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N<sub>3</sub>, CN, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, NH<sub>2</sub>, NH(CH<sub>3</sub>) or N(CH<sub>3</sub>)<sub>2</sub>;

R<sup>6A</sup> and R<sup>6B</sup> are independently selected alkyl or, together with the N to which they are attached, R<sup>6C</sup>;

R<sup>6C</sup> is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH<sub>2</sub> moiety unreplaced or replaced with O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup>;

R<sup>8</sup> is phenyl, which is unfused or fused with R<sup>8A</sup>; R<sup>8A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>9</sup> is heteroaryl, which is unfused or fused with R<sup>9A</sup>; R<sup>9A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>10A</sup>; R<sup>10A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>11</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup>, SR<sup>12</sup>, S(O)R<sup>12</sup>, SO<sub>2</sub>R<sup>12</sup>, C(O)R<sup>12</sup>, CO(O)R<sup>12</sup>, OC(O)R<sup>12</sup>, OC(O)OR<sup>12</sup>, NH<sub>2</sub>, NHR<sup>12</sup>, N(R<sup>12</sup>)<sub>2</sub>, NHC(O)R<sup>12</sup>, NR<sup>12</sup>C(O)R<sup>12</sup>, NHS(O)<sub>2</sub>R<sup>12</sup>, NR<sup>12</sup>S(O)<sub>2</sub>R<sup>12</sup>, NHC(O)OR<sup>12</sup>, NR<sup>12</sup>C(O)OR<sup>12</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>12</sup>, NHC(O)N(R<sup>12</sup>)<sub>2</sub>, NR<sup>12</sup>C(O)NHR<sup>12</sup>, NR<sup>12</sup>C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>12</sup>, C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>12</sup>, C(O)NHSO<sub>2</sub>R<sup>12</sup>, C(O)NR<sup>12</sup>SO<sub>2</sub>R<sup>12</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>12</sup>, SO<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>12</sup>, C(N)N(R<sup>12</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>12</sup> is R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> or R<sup>16</sup>;

R<sup>13</sup> is phenyl, which is unfused or fused with R<sup>13A</sup>; R<sup>13A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>14</sup> is heteroaryl, which is unfused or fused with R<sup>14A</sup>; R<sup>14A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>15</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R<sup>15A</sup>; R<sup>15A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>16</sup> is alkyl, alkenyl or alkynyl;

R<sup>17</sup> is R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> or R<sup>21</sup>;

R<sup>18</sup> is phenyl, which is unfused or fused with R<sup>18A</sup>; R<sup>18A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>19</sup> is heteroaryl, which is unfused or fused with R<sup>19A</sup>; R<sup>19A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>20</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R<sup>20A</sup>; R<sup>20A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>21</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, OR<sup>22</sup>, SR<sup>22</sup>, S(O)R<sup>22</sup>, SO<sub>2</sub>R<sup>22</sup>, COR<sup>22</sup>, CO(O)R<sup>22</sup>, OC(O)R<sup>22</sup>, OC(O)OR<sup>22</sup>, NH<sub>2</sub>, NHR<sup>22</sup>, N(R<sup>22</sup>)<sub>2</sub>, NHC(O)R<sup>22</sup>, NR<sup>22</sup>C(O)R<sup>22</sup>, NHS(O)<sub>2</sub>R<sup>22</sup>, NR<sup>22</sup>S(O)<sub>2</sub>R<sup>22</sup>, NHC(O)OR<sup>22</sup>, NR<sup>22</sup>C(O)OR<sup>22</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>22</sup>, NHC(O)N(R<sup>22</sup>)<sub>2</sub>, NR<sup>22</sup>C(O)NHR<sup>22</sup>, NR<sup>22</sup>C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>22</sup>, C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>22</sup>, C(O)NHSO<sub>2</sub>R<sup>22</sup>, C(O)NR<sup>22</sup>SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>22</sup>, SO<sub>2</sub>N(R<sup>22</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)

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NHR<sup>22</sup>, C(N)N(R<sup>22</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>23</sup>, R<sup>24</sup> or R<sup>25</sup>;

R<sup>23</sup> is phenyl, which is unfused or fused with R<sup>23A</sup>; R<sup>23A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>24</sup> is heteroarene, which is unfused or fused with R<sup>24A</sup>; R<sup>24A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>25</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>25A</sup>; R<sup>25A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z<sup>1</sup> is R<sup>26</sup> or R<sup>27</sup>;

Z<sup>2</sup> is R<sup>28</sup>, R<sup>29</sup> or R<sup>30</sup>;

Z<sup>1A</sup> and Z<sup>2A</sup> are both absent or are taken together to form CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub> or Z<sup>12A</sup>;

Z<sup>12A</sup> is C<sub>2</sub>-C<sub>6</sub>-alkylene having one or two CH<sub>2</sub> moieties replaced by NH, N(CH<sub>3</sub>), S, S(O) or SO<sub>2</sub>;

L<sup>1</sup> is a R<sup>37</sup>, OR<sup>37</sup>, SR<sup>37</sup>, S(O)R<sup>37</sup>, SO<sub>2</sub>R<sup>37</sup>, C(O)R<sup>37</sup>, CO(O)R<sup>37</sup>, OC(O)R<sup>37</sup>, OC(O)OR<sup>37</sup>, NHR<sup>37</sup>, C(O)NH, C(O)NR<sup>37</sup>, C(O)NHOR<sup>37</sup>, C(O)NHSO<sub>2</sub>R<sup>37</sup>, SO<sub>2</sub>NH, SO<sub>2</sub>NHR<sup>37</sup>, C(N)NH, C(N)NHR<sup>37</sup>;

R<sup>26</sup> is phenylene, which is unfused or fused with R<sup>26A</sup>; R<sup>26A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>27</sup> is heteroarylene, which is unfused or fused with R<sup>27A</sup>; R<sup>27A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>28</sup> is phenylene, which is unfused or fused with R<sup>28A</sup>; R<sup>28A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>29</sup> is heteroarylene, which is unfused or fused with R<sup>29A</sup>; R<sup>29A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>30</sup> is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R<sup>30A</sup>; R<sup>30A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>37</sup> is a bond or R<sup>37A</sup>;

R<sup>37A</sup> is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R<sup>37B</sup>, OR<sup>37B</sup>, SR<sup>37B</sup>, S(O)R<sup>37B</sup>, SO<sub>2</sub>R<sup>37B</sup>, C(O)R<sup>37B</sup>, CO(O)R<sup>37B</sup>, OC(O)R<sup>37B</sup>, OC(O)OR<sup>37B</sup>, NH<sub>2</sub>, NHR<sup>37B</sup>, N(R<sup>37B</sup>)<sub>2</sub>, NHC(O)R<sup>37B</sup>, NR<sup>37B</sup>C(O)R<sup>37B</sup>, NHS(O)<sub>2</sub>R<sup>37B</sup>, NR<sup>37B</sup>S(O)<sub>2</sub>R<sup>37B</sup>, NHC(O)OR<sup>37B</sup>, NR<sup>37B</sup>C(O)OR<sup>37B</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>37B</sup>, NHC(O)N(R<sup>37B</sup>)<sub>2</sub>, NR<sup>37B</sup>C(O)NHR<sup>37B</sup>, NR<sup>37B</sup>C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>37B</sup>, C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>37B</sup>, C(O)NHSO<sub>2</sub>R<sup>37B</sup>, C(O)NR<sup>37B</sup>SO<sub>2</sub>R<sup>37B</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>37B</sup>, SO<sub>2</sub>N(R<sup>37B</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>37B</sup>, C(N)N(R<sup>37B</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br and I substituents; R<sup>37B</sup> is alkyl, alkenyl, alkynyl, or R<sup>37C</sup>;

R<sup>37C</sup> is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

Z<sup>3</sup> is R<sup>38</sup>, R<sup>39</sup> or R<sup>40</sup>;

R<sup>38</sup> is phenyl, which is unfused or fused with R<sup>38A</sup>; R<sup>38A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>39</sup> is heteroaryl, which is unfused or fused with R<sup>39A</sup>; R<sup>39A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>40</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>40A</sup>; R<sup>40A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;



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wherein the moieties represented by  $R^{26}$  and  $R^{27}$  are substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are absent) or further substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are present) with  $R^{41}$ ,  $OR^{41}$ ,  $SR^{41}$ ,  $S(O)R^{41}$ ,  $SO_2R^{41}$ ,  $CO(O)R^{41}$ ,  $OC(O)R^{41}$ ,  $OC(O)OR^{41}$ ,  $NHR^{41}$ ,  $N(R^{41})_2$ ,  $NHC(O)R^{41}$ ,  $NR^{41}C(O)R^{41}$ ,  $NHS(O)_2R^{41}$ ,  $NR^{41}S(O)_2R^{41}$ ,  $NHC(O)OR^{41}$ ,  $NR^{41}C(O)OR^{41}$ ,  $NHC(O)NHR^{41}$ ,  $NHC(O)N(R^{41})_2$ ,  $NR^{41}C(O)NHR^{41}$ ,  $NR^{41}C(O)N(R^{41})_2$ ,  $C(O)NHR^{41}$ ,  $C(O)N(R^{41})_2$ ,  $C(O)NHOR^{41}$ ,  $C(O)NHSO_2R^{41}$ ,  $C(O)NR^{41}SO_2R^{41}$ ,  $SO_2NHR^{41}$ ,  $SO_2N(R^{41})_2$ ,  $C(N)NHR^{41}$ , or  $C(N)N(R^{41})_2$ ;

$R^{41}$  is heteroaryl, which is fused with  $R^{43A}$ ;  $R^{43A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused or fused with benzene, heteroarene or  $R^{43B}$ ;  $R^{43B}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by  $E^1$  and  $Y^1$  together,  $Y^1$  and  $B^1$  together,  $A^2$  and  $B^1$  together,  $A^2$  and  $D^1$  together,  $R^{1A}$ ,  $R^2$ ,  $R^{2A}$ ,  $R^3$ ,  $R^{3A}$ ,  $R^4$ ,  $R^{4A}$ ,  $R^6$ ,  $R^{6C}$ ,  $R^8$ ,  $R^{8A}$ ,  $R^9$ ,  $R^{9A}$ ,  $R^{10}$ ,  $R^{10A}$ ,  $R^{13}$ ,  $R^{13A}$ ,  $R^{14}$ ,  $R^{14A}$ ,  $R^{15}$ ,  $R^{15A}$ ,  $R^{18}$ ,  $R^{18A}$ ,  $R^{19}$ ,  $R^{19A}$ ,  $R^{20}$ ,  $R^{20A}$ ,  $R^{23}$ ,  $R^{23A}$ ,  $R^{24}$ ,  $R^{24A}$ ,  $R^{25}$ ,  $R^{25A}$ ,  $R^{26}$ ,  $R^{26A}$ ,  $R^{27}$ ,  $R^{27A}$ ,  $R^{28}$ ,  $R^{28A}$ ,  $R^{29}$ ,  $R^{29A}$ ,  $R^{30}$ ,  $R^{30A}$ ,  $R^{37B}$ ,  $R^{38}$ ,  $R^{38A}$ ,  $R^{39}$ ,  $R^{39A}$ ,  $R^{40}$ , and  $R^{40A}$  are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SR^{57}$ ,  $S(O)R^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $OC(O)R^{57}$ ,  $OC(O)OR^{57}$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NR^{57}C(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $NR^{57}S(O)_2R^{57}$ ,  $NHC(O)OR^{57}$ ,  $NR^{57}C(O)OR^{57}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{57}$ ,  $NHC(O)N(R^{57})_2$ ,  $NR^{57}C(O)NHR^{57}$ ,  $NR^{57}C(O)N(R^{57})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{57}$ ,  $C(O)N(R^{57})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{57}$ ,  $C(O)NHSO_2R^{57}$ ,  $C(O)NR^{57}SO_2R^{57}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{57}$ ,  $SO_2N(R^{57})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{57}$ ,  $C(N)N(R^{57})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl, which is unfused or fused with  $R^{58A}$ ;  $R^{58A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{59}$  is heteroaryl, which is unfused or fused with  $R^{59A}$ ;  $R^{59A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{60}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{60A}$ ;  $R^{60A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{61}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $SR^{62}$ ,  $S(O)R^{62}$ ,  $SO_2R^{62}$ ,  $C(O)R^{62}$ ,  $CO(O)R^{62}$ ,  $OC(O)R^{62}$ ,  $OC(O)OR^{62}$ ,  $NH_2$ ,  $NHR^{62}$ ,  $N(R^{62})_2$ ,  $NHC(O)R^{62}$ ,  $NR^{62}C(O)R^{62}$ ,  $NHS(O)_2R^{62}$ ,  $NR^{62}S(O)_2R^{62}$ ,  $NHC(O)OR^{62}$ ,  $NR^{62}C(O)OR^{62}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{62}$ ,  $NHC(O)N(R^{62})_2$ ,  $NR^{62}C(O)NHR^{62}$ ,  $NR^{62}C(O)N(R^{62})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{62}$ ,  $C(O)N(R^{62})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{62}$ ,  $C(O)NHSO_2R^{62}$ ,  $C(O)NR^{62}SO_2R^{62}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{62}$ ,  $SO_2N(R^{62})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{62}$ ,  $C(N)N(R^{62})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{62}$  is  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$  or  $R^{66}$ ;

$R^{63}$  is phenyl, which is unfused or fused with  $R^{63A}$ ;  $R^{63A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{64}$  is heteroaryl, which is unfused or fused with  $R^{64A}$ ;  $R^{64A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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$R^{65}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with  $R^{65A}$ ;  $R^{65A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{66}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{67}$ ,  $OR^{67}$ ,  $SR^{67}$ ,  $S(O)R^{67}$ ,  $SO_2R^{67}$ ,  $C(O)R^{67}$ ,  $CO(O)R^{67}$ ,  $OC(O)R^{67}$ ,  $OC(O)OR^{67}$ ,  $NH_2$ ,  $NHR^{67}$ ,  $N(R^{67})_2$ ,  $NHC(O)R^{67}$ ,  $NR^{67}C(O)R^{67}$ ,  $NHS(O)_2R^{67}$ ,  $NR^{67}S(O)_2R^{67}$ ,  $NHC(O)OR^{67}$ ,  $NR^{67}C(O)OR^{67}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{67}$ ,  $NHC(O)N(R^{67})_2$ ,  $NR^{67}C(O)NHR^{67}$ ,  $NR^{67}C(O)N(R^{67})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{67}$ ,  $C(O)N(R^{67})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{67}$ ,  $C(O)NHSO_2R^{67}$ ,  $C(O)NR^{67}SO_2R^{67}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{67}$ ,  $SO_2N(R^{67})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{67}$ ,  $C(N)N(R^{67})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$  substituents;

$R^{67}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$ ,  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$ , and  $R^{67}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $OR^{68}$ ,  $SR^{68}$ ,  $S(O)R^{68}$ ,  $SO_2R^{68}$ ,  $C(O)R^{68}$ ,  $CO(O)R^{68}$ ,  $OC(O)R^{68}$ ,  $OC(O)OR^{68}$ ,  $NH_2$ ,  $NHR^{68}$ ,  $N(R^{68})_2$ ,  $NHC(O)R^{68}$ ,  $NR^{68}C(O)R^{68}$ ,  $NHS(O)_2R^{68}$ ,  $NR^{68}S(O)_2R^{68}$ ,  $NHC(O)OR^{68}$ ,  $NR^{68}C(O)OR^{68}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{68}$ ,  $NHC(O)N(R^{68})_2$ ,  $NR^{68}C(O)NHR^{68}$ ,  $NR^{68}C(O)N(R^{68})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{68}$ ,  $C(O)N(R^{68})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{68}$ ,  $C(O)NHSO_2R^{68}$ ,  $C(O)NR^{68}SO_2R^{68}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{68}$ ,  $SO_2N(R^{68})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{68}$ ,  $C(N)N(R^{68})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{68}$  is  $R^{69}$ ,  $R^{70}$ ,  $R^{71}$  or  $R^{72}$ ;

$R^{69}$  is phenyl, which is unfused or fused with  $R^{69A}$ ;  $R^{69A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{70}$  is heteroaryl, which is unfused or fused with  $R^{70A}$ ;  $R^{70A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{71}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{71A}$ ;  $R^{71A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{72}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{73}$ ,  $OR^{73}$ ,  $SR^{73}$ ,  $S(O)R^{73}$ ,  $SO_2R^{73}$ ,  $C(O)R^{73}$ ,  $CO(O)R^{73}$ ,  $OC(O)R^{73}$ ,  $OC(O)OR^{73}$ ,  $NH_2$ ,  $NHR^{73}$ ,  $N(R^{73})_2$ ,  $NHC(O)R^{73}$ ,  $NR^{73}C(O)R^{73}$ ,  $NHS(O)_2R^{73}$ ,  $NR^{73}S(O)_2R^{73}$ ,  $NHC(O)OR^{73}$ ,  $NR^{73}C(O)OR^{73}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{73}$ ,  $NHC(O)N(R^{73})_2$ ,  $NR^{73}C(O)NHR^{73}$ ,  $NR^{73}C(O)N(R^{73})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{73}$ ,  $C(O)N(R^{73})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{73}$ ,  $C(O)NHSO_2R^{73}$ ,  $C(O)NR^{73}SO_2R^{73}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{73}$ ,  $SO_2N(R^{73})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{73}$ ,  $C(N)N(R^{73})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{73}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by  $R^{69}$ ,  $R^{70}$ , and  $R^{71}$  are unsubstituted or substituted with one or two or three or four of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $C(O)NHOH$ ,  $SO_2NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ .



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Another embodiment of this invention pertains to compounds of Formula (I), wherein

A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

B<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

D<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

E<sup>1</sup> is H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, C(O)OH, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, C(O)R<sup>17</sup>, C(O)OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, NH<sub>2</sub>, NHR<sup>17</sup>, N(R<sup>17</sup>)<sub>2</sub>, NHC(O)R<sup>17</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>17</sup>, C(O)N(R<sup>17</sup>)<sub>2</sub>, NHC(O)R<sup>17</sup> or NHC(O)R<sup>17</sup>; or

E<sup>1</sup> and Y<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, B<sup>1</sup>, and D<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>,

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C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

A<sup>2</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>; or

A<sup>2</sup> and D<sup>1</sup>, together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

B<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are independently selected H, R<sup>1</sup>, OR<sup>1</sup>, SR<sup>1</sup>, S(O)R<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, C(O)R<sup>1</sup>, C(O)OR<sup>1</sup>, OC(O)R<sup>1</sup>, NHR<sup>1</sup>, N(R<sup>1</sup>)<sub>2</sub>, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>SO<sub>2</sub>NHR<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, C(O)NHNOR<sup>1</sup>, C(O)NHSO<sub>2</sub>R<sup>1</sup>, C(NH)NH<sub>2</sub>, C(NH)NHR<sup>1</sup>, C(NH)N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>NHR<sup>1</sup>, NH<sub>2</sub>SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, N(CH<sub>3</sub>)SO<sub>2</sub>N(CH<sub>3</sub>)R<sup>1</sup>, F, Cl, Br, I, CN, NO<sub>2</sub>, N<sub>3</sub>, OH, C(O)H, CHNOH, CH(NOCH<sub>3</sub>), CF<sub>3</sub>, C(O)OH, C(O)NH<sub>2</sub> or C(O)OR<sup>1,4</sup>;

G<sup>1</sup> is H, or C(O)OR;

R is alkyl;

R<sup>1</sup> is R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup>;

R<sup>1,4</sup> is cycloalkyl, cycloalkenyl or cycloalkynyl;

R<sup>2</sup> is phenyl, which is unfused or fused with R<sup>2,4</sup>; R<sup>2,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>3</sup> is heteroaryl, which is unfused or fused with R<sup>3,4</sup>; R<sup>3,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>4,4</sup>; R<sup>4,4</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>5</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently

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selected  $R^6$ ,  $NC(R^{6A})(R^{6B})$ ,  $R^7$ ,  $OR^7$ ,  $SR^1$ ,  $S(O)R^7$ ,  $SO_2R^7$ ,  $NHR^7$ ,  $N(R^7)_2$ ,  $C(O)R^7$ ,  $C(O)NH_2$ ,  $C(O)NHR^7$ ,  $C(O)N(R^7)_2$ ,  $NHC(O)R^7$ ,  $NR^7C(O)R^7$ ,  $NHSO_2R^7$ ,  $NHC(O)OR^7$ ,  $SO_2NH_2$ ,  $SO_2NHR^7$ ,  $SO_2N(R^7)_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^7$ ,  $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$ ,  $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NHR^7$ ,  $OH$ ,  $(O)$ ,  $C(O)OH$ ,  $N_3$ ,  $CN$ ,  $NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^6$  is  $C_2$ - $C_5$ -spiroalkyl, each of which is unsubstituted or substituted with  $OH$ ,  $(O)$ ,  $N_3$ ,  $CN$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $NH_2$ ,  $NH(CH_3)$  or  $N(CH_3)_2$ ;

$R^{6A}$  and  $R^{6B}$  are independently selected alkyl or, together with the  $N$  to which they are attached,  $R^{6C}$ ;

$R^{6C}$  is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one  $CH_2$  moiety unreplaced or replaced with  $O$ ,  $C(O)$ ,  $CNOH$ ,  $CNOCH_3$ ,  $S$ ,  $S(O)$ ,  $SO_2$  or  $NH$ ;

$R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$  or  $R^{11}$ ;

$R^8$  is phenyl, which is unfused or fused with  $R^{8A}$ ;  $R^{8A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^9$  is heteroaryl, which is unfused or fused with  $R^{9A}$ ;  $R^{9A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{10}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{10A}$ ;  $R^{10A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{11}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{12}$ ,  $OR^{12}$ ,  $SR^{12}$ ,  $S(O)R^{12}$ ,  $SO_2R^{12}$ ,  $C(O)R^{12}$ ,  $CO(O)R^{12}$ ,  $OC(O)R^{12}$ ,  $OC(O)OR^{12}$ ,  $NH_2$ ,  $NHR^{12}$ ,  $N(R^{12})_2$ ,  $NHC(O)R^{12}$ ,  $NR^{12}C(O)R^{12}$ ,  $NHS(O)_2R^{12}$ ,  $NR^{12}S(O)_2R^{12}$ ,  $NHC(O)OR^{12}$ ,  $NR^{12}C(O)OR^{12}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{12}$ ,  $NHC(O)N(R^{12})_2$ ,  $NR^{12}C(O)NHR^{12}$ ,  $NR^{12}C(O)N(R^{12})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{12}$ ,  $C(O)N(R^{12})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{12}$ ,  $C(O)NHSO_2R^{12}$ ,  $C(O)NR^{12}SO_2R^{12}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{12}$ ,  $SO_2N(R^{12})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{12}$ ,  $C(N)N(R^{12})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{12}$  is  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$  or  $R^{16}$ ;

$R^{13}$  is phenyl, which is unfused or fused with  $R^{13A}$ ;  $R^{13A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{14}$  is heteroaryl, which is unfused or fused with  $R^{14A}$ ;  $R^{14A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{15}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with  $R^{15A}$ ;  $R^{15A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{16}$  is alkyl, alkenyl or alkynyl;

$R^{17}$  is  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  or  $R^{21}$ ;

$R^{18}$  is phenyl, which is unfused or fused with  $R^{18A}$ ;  $R^{18A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{19}$  is heteroaryl, which is unfused or fused with  $R^{19A}$ ;  $R^{19A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{20}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with  $R^{20A}$ ;  $R^{20A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{21}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{22}$ ,  $OR^{22}$ ,  $SR^{22}$ ,  $S(O)R^{22}$ ,  $SO_2R^{22}$ ,  $C(O)R^{22}$ ,  $CO(O)R^{22}$ ,  $OC(O)R^{22}$ ,  $OC(O)OR^{22}$ ,  $NH_2$ ,  $NHR^{22}$ ,  $N(R^{22})_2$ ,

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$NHC(O)R^{22}$ ,  $NR^{22}C(O)R^{22}$ ,  $NHS(O)_2R^{22}$ ,  $NR^{22}S(O)_2R^{22}$ ,  $NHC(O)OR^{22}$ ,  $NR^{22}C(O)OR^{22}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{22}$ ,  $NHC(O)N(R^{22})_2$ ,  $NR^{22}C(O)NHR^{22}$ ,  $NR^{22}C(O)N(R^{22})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{22}$ ,  $C(O)N(R^{22})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{22}$ ,  $C(O)NHSO_2R^{22}$ ,  $C(O)NR^{22}SO_2R^{22}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{22}$ ,  $SO_2N(R^{22})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{22}$ ,  $C(N)N(R^{22})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{22}$  is  $R^{23}$ ,  $R^{24}$  or  $R^{25}$ ;

$R^{23}$  is phenyl, which is unfused or fused with  $R^{23A}$ ;  $R^{23A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{24}$  is heteroarene, which is unfused or fused with  $R^{24A}$ ;

$R^{24A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{25}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{25A}$ ;  $R^{25A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$Z^1$  is  $R^{26}$  or  $R^{27}$ ;

$Z^2$  is  $R^{28}$ ,  $R^{29}$  or  $R^{30}$ ;

$Z^{1A}$  and  $Z^{2A}$  are both absent or are taken together to form  $CH_2$ ,  $CH_2CH_2$  or  $Z^{12A}$ ;

$Z^{12A}$  is  $C_2$ - $C_6$ -alkylene having one or two  $CH_2$  moieties replaced by  $NH$ ,  $N(CH_3)$ ,  $S$ ,  $S(O)$  or  $SO_2$ ;

$L^1$  is a  $R^{37}$ ,  $OR^{37}$ ,  $SR^{37}$ ,  $S(O)R^{37}$ ,  $SO_2R^{37}$ ,  $C(O)R^{37}$ ,  $CO(O)R^{37}$ ,  $OC(O)R^{37}$ ,  $OC(O)OR^{37}$ ,  $NHR^{37}$ ,  $C(O)NH$ ,  $C(O)NR^{37}$ ,  $C(O)NHOR^{37}$ ,  $C(O)NHSO_2R^{37}$ ,  $SO_2NH$ ,  $SO_2NHR^{37}$ ,  $C(N)NH$ ,  $C(N)NHR^{37}$ ;

$R^{26}$  is phenylene, which is unfused or fused with  $R^{26A}$ ;  $R^{26A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{27}$  is heteroarylene, which is unfused or fused with  $R^{27A}$ ;  $R^{27A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{28}$  is phenylene, which is unfused or fused with  $R^{28A}$ ;  $R^{28A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{29}$  is heteroarylene, which is unfused or fused with  $R^{29A}$ ;  $R^{29A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{30}$  is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with  $R^{30A}$ ;  $R^{30A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{37}$  is a bond or  $R^{37A}$ ;

$R^{37A}$  is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected  $R^{37B}$ ,  $OR^{37B}$ ,  $SR^{37B}$ ,  $S(O)R^{37B}$ ,  $SO_2R^{37B}$ ,

$C(O)R^{37B}$ ,  $CO(O)R^{37B}$ ,  $OC(O)R^{37B}$ ,  $OC(O)OR^{37B}$ ,  $NH_2$ ,  $NHR^{37B}$ ,  $N(R^{37B})_2$ ,  $NHC(O)R^{37B}$ ,  $NR^{37B}C(O)R^{37B}$ ,  $NHS(O)_2R^{37B}$ ,  $NR^{37B}S(O)_2R^{37B}$ ,  $NHC(O)OR^{37B}$ ,  $NR^{37B}C(O)OR^{37B}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{37B}$ ,  $NHC(O)N(R^{37B})_2$ ,  $NR^{37B}C(O)NHR^{37B}$ ,  $NR^{37B}C(O)N(R^{37B})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{37B}$ ,  $C(O)N(R^{37B})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{37B}$ ,  $C(O)NHSO_2R^{37B}$ ,  $C(O)NR^{37B}SO_2R^{37B}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{37B}$ ,  $SO_2N(R^{37B})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{37B}$ ,  $C(N)N(R^{37B})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  and  $I$  substituents;

$R^{37B}$  is alkyl, alkenyl, alkynyl, or  $R^{37C}$ ;

$R^{37C}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

$Z^3$  is  $R^{38}$ ,  $R^{39}$  or  $R^{40}$ ;

$R^{38}$  is phenyl, which is unfused or fused with  $R^{38A}$ ;  $R^{38A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

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R<sup>39</sup> is heteroaryl, which is unfused or fused with R<sup>39A</sup>; R<sup>39A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>40</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>40A</sup>; R<sup>40A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by R<sup>26</sup> and R<sup>27</sup> are substituted (i.e., if Z<sup>1A</sup> and Z<sup>2A</sup> are absent) or further substituted (i.e., if Z<sup>1A</sup> and Z<sup>2A</sup> are present) with R<sup>41</sup>, OR<sup>41</sup>, SR<sup>41</sup>, S(O)R<sup>41</sup>, SO<sub>2</sub>R<sup>41</sup>, C(O)R<sup>41</sup>, CO(O)R<sup>41</sup>, OC(O)R<sup>41</sup>, OC(O)OR<sup>41</sup>, NHR<sup>41</sup>, N(R<sup>41</sup>)<sub>2</sub>, NHC(O)R<sup>41</sup>, NR<sup>41</sup>C(O)R<sup>41</sup>, NHS(O)<sub>2</sub>R<sup>41</sup>, NR<sup>41</sup>S(O)<sub>2</sub>R<sup>41</sup>, NHC(O)OR<sup>41</sup>, NR<sup>41</sup>C(O)OR<sup>41</sup>, NHC(O)NHR<sup>41</sup>, NHC(O)N(R<sup>41</sup>)<sub>2</sub>, NR<sup>41</sup>C(O)NHR<sup>41</sup>, NR<sup>41</sup>C(O)N(R<sup>41</sup>)<sub>2</sub>, C(O)NHR<sup>41</sup>, C(O)N(R<sup>41</sup>)<sub>2</sub>, C(O)NHOR<sup>41</sup>, C(O)NHSO<sub>2</sub>R<sup>41</sup>, C(O)NR<sup>41</sup>SO<sub>2</sub>R<sup>41</sup>, SO<sub>2</sub>NHR<sup>41</sup>, SO<sub>2</sub>N(R<sup>41</sup>)<sub>2</sub>, C(N)NHR<sup>41</sup>, or C(N)N(R<sup>41</sup>)<sub>2</sub>;

R<sup>41</sup> is heteroaryl, which is fused with R<sup>43A</sup>; R<sup>43A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is unfused;

wherein the cyclic moieties represented by E<sup>1</sup> and Y<sup>1</sup> together, Y<sup>1</sup> and B<sup>1</sup> together, A<sup>2</sup> and B<sup>1</sup> together, A<sup>2</sup> and D<sup>1</sup> together, R<sup>1A</sup>, R<sup>2</sup>, R<sup>1A</sup>, R<sup>2</sup>, R<sup>2A</sup>, R<sup>3</sup>, R<sup>3A</sup>, R<sup>4</sup>, R<sup>4A</sup>, R<sup>6</sup>, R<sup>6C</sup>, R<sup>8</sup>, R<sup>8A</sup>, R<sup>9</sup>, R<sup>9A</sup>, R<sup>10</sup>, R<sup>10A</sup>, R<sup>13</sup>, R<sup>13A</sup>, R<sup>14</sup>, R<sup>14A</sup>, R<sup>15</sup>, R<sup>15A</sup>, R<sup>18</sup>, R<sup>18A</sup>, R<sup>19</sup>, R<sup>19A</sup>, R<sup>20</sup>, R<sup>20A</sup>, R<sup>23</sup>, R<sup>23A</sup>, R<sup>24</sup>, R<sup>24A</sup>, R<sup>25</sup>, R<sup>25A</sup>, R<sup>26</sup>, R<sup>26A</sup>, R<sup>27</sup>, R<sup>27A</sup>, R<sup>28</sup>, R<sup>28A</sup>, R<sup>29</sup>, R<sup>29A</sup>, R<sup>30</sup>, R<sup>30A</sup>, R<sup>37B</sup>, R<sup>38</sup>, R<sup>38A</sup>, R<sup>39</sup>, R<sup>39A</sup>, R<sup>40</sup>, and R<sup>40A</sup> are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SR<sup>57</sup>, S(O)R<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, OC(O)R<sup>57</sup>, OC(O)OR<sup>57</sup>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NR<sup>57</sup>C(O)R<sup>57</sup>, NHS(O)<sub>2</sub>R<sup>57</sup>, NR<sup>57</sup>S(O)<sub>2</sub>R<sup>57</sup>, NHC(O)OR<sup>57</sup>, NR<sup>57</sup>C(O)OR<sup>57</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>57</sup>, NHC(O)N(R<sup>57</sup>)<sub>2</sub>, NR<sup>57</sup>C(O)NHR<sup>57</sup>, NR<sup>57</sup>C(O)N(R<sup>57</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, C(O)NHOR<sup>57</sup>, C(O)NHSO<sub>2</sub>R<sup>57</sup>, C(O)NR<sup>57</sup>SO<sub>2</sub>R<sup>57</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>57</sup>, SO<sub>2</sub>N(R<sup>57</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>57</sup>, C(N)N(R<sup>57</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;

R<sup>57</sup> is R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup> or R<sup>61</sup>;

R<sup>58</sup> is phenyl, which is unfused or fused with R<sup>58A</sup>; R<sup>58A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>59</sup> is heteroaryl, which is unfused or fused with R<sup>59A</sup>; R<sup>59A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>60</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>60A</sup>; R<sup>60A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>61</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, SR<sup>62</sup>, S(O)R<sup>62</sup>, SO<sub>2</sub>R<sup>62</sup>, C(O)R<sup>62</sup>, CO(O)R<sup>62</sup>, OC(O)R<sup>62</sup>, OC(O)OR<sup>62</sup>, NH<sub>2</sub>, NHR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, NHC(O)R<sup>62</sup>, NR<sup>62</sup>C(O)R<sup>62</sup>, NHS(O)<sub>2</sub>R<sup>62</sup>, NR<sup>62</sup>S(O)<sub>2</sub>R<sup>62</sup>, NHC(O)OR<sup>62</sup>, NR<sup>62</sup>C(O)OR<sup>62</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>62</sup>, NHC(O)N(R<sup>62</sup>)<sub>2</sub>, NR<sup>62</sup>C(O)NHR<sup>62</sup>, NR<sup>62</sup>C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>62</sup>, C(O)N(R<sup>62</sup>)<sub>2</sub>, C(O)NHOR<sup>62</sup>, C(O)NHSO<sub>2</sub>R<sup>62</sup>, C(O)NR<sup>62</sup>SO<sub>2</sub>R<sup>62</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>62</sup>, SO<sub>2</sub>N(R<sup>62</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>62</sup>, C(N)N(R<sup>62</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or T;

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R<sup>62</sup> is R<sup>63</sup>, R<sup>64</sup>, R<sup>65</sup> or R<sup>66</sup>;

R<sup>63</sup> is phenyl, which is unfused or fused with R<sup>63A</sup>; R<sup>63A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>64</sup> is heteroaryl, which is unfused or fused with R<sup>64A</sup>; R<sup>64A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>65</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>65A</sup>; R<sup>65A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>66</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>67</sup>, OR<sup>67</sup>, SR<sup>67</sup>, S(O)R<sup>67</sup>, SO<sub>2</sub>R<sup>67</sup>, C(O)R<sup>67</sup>, CO(O)R<sup>67</sup>, OC(O)R<sup>67</sup>, OC(O)OR<sup>67</sup>, NH<sub>2</sub>, NHR<sup>67</sup>, N(R<sup>67</sup>)<sub>2</sub>, NHC(O)R<sup>67</sup>, NR<sup>67</sup>C(O)R<sup>67</sup>, NHS(O)<sub>2</sub>R<sup>67</sup>, NR<sup>67</sup>S(O)<sub>2</sub>R<sup>67</sup>, NHC(O)OR<sup>67</sup>, NR<sup>67</sup>C(O)OR<sup>67</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>67</sup>, NHC(O)N(R<sup>67</sup>)<sub>2</sub>, NR<sup>67</sup>C(O)NHR<sup>67</sup>, NR<sup>67</sup>C(O)N(R<sup>67</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>67</sup>, C(O)N(R<sup>67</sup>)<sub>2</sub>, C(O)NHOR<sup>67</sup>, C(O)NHSO<sub>2</sub>R<sup>67</sup>, C(O)NR<sup>67</sup>SO<sub>2</sub>R<sup>67</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>67</sup>, SO<sub>2</sub>N(R<sup>67</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>67</sup>, C(N)N(R<sup>67</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I substituents;

R<sup>67</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup>, R<sup>61</sup>, R<sup>64</sup>, R<sup>65</sup>, and R<sup>67</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, OR<sup>68</sup>, SR<sup>68</sup>, S(O)R<sup>68</sup>, SO<sub>2</sub>R<sup>68</sup>, C(O)R<sup>68</sup>, CO(O)R<sup>68</sup>, OC(O)R<sup>68</sup>, OC(O)OR<sup>68</sup>, NH<sub>2</sub>, NHR<sup>68</sup>, N(R<sup>68</sup>)<sub>2</sub>, NHC(O)R<sup>68</sup>, NR<sup>68</sup>C(O)R<sup>68</sup>, NHS(O)<sub>2</sub>R<sup>68</sup>, NR<sup>68</sup>S(O)<sub>2</sub>R<sup>68</sup>, NHC(O)OR<sup>68</sup>, NR<sup>68</sup>C(O)OR<sup>68</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>68</sup>, NHC(O)N(R<sup>68</sup>)<sub>2</sub>, NR<sup>68</sup>C(O)NHR<sup>68</sup>, NR<sup>68</sup>C(O)N(R<sup>68</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>68</sup>, C(O)N(R<sup>68</sup>)<sub>2</sub>, C(O)NHOR<sup>68</sup>, C(O)NHSO<sub>2</sub>R<sup>68</sup>, C(O)NR<sup>68</sup>SO<sub>2</sub>R<sup>68</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>68</sup>, SO<sub>2</sub>N(R<sup>68</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>68</sup>, C(N)N(R<sup>68</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>68</sup> is R<sup>69</sup>, R<sup>70</sup>, R<sup>71</sup> or R<sup>72</sup>;

R<sup>69</sup> is phenyl, which is unfused or fused with R<sup>69A</sup>; R<sup>69A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>70</sup> is heteroaryl, which is unfused or fused with R<sup>70A</sup>; R<sup>70A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>71</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>71A</sup>; R<sup>71A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>72</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>73</sup>, OR<sup>73</sup>, SR<sup>73</sup>, S(O)R<sup>73</sup>, SO<sub>2</sub>R<sup>73</sup>, C(O)R<sup>73</sup>, CO(O)R<sup>73</sup>, OC(O)R<sup>73</sup>, OC(O)OR<sup>73</sup>, NH<sub>2</sub>, NHR<sup>73</sup>, N(R<sup>73</sup>)<sub>2</sub>, NHC(O)R<sup>73</sup>, NR<sup>73</sup>C(O)R<sup>73</sup>, NHS(O)<sub>2</sub>R<sup>73</sup>, NR<sup>73</sup>S(O)<sub>2</sub>R<sup>73</sup>, NHC(O)OR<sup>73</sup>, NR<sup>73</sup>C(O)OR<sup>73</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>73</sup>, NHC(O)N(R<sup>73</sup>)<sub>2</sub>, NR<sup>73</sup>C(O)NHR<sup>73</sup>, NR<sup>73</sup>C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>73</sup>, C(O)N(R<sup>73</sup>)<sub>2</sub>, C(O)NHOR<sup>73</sup>, C(O)NHSO<sub>2</sub>R<sup>73</sup>, C(O)NR<sup>73</sup>SO<sub>2</sub>R<sup>73</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>73</sup>, SO<sub>2</sub>N(R<sup>73</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>73</sup>, C(N)N(R<sup>73</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>73</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and



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wherein the moieties represented by  $R^{69}$ ,  $R^{70}$ , and  $R^{71}$  are unsubstituted or substituted with one or two or three or four of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $C(O)NHOH$ ,  $SO_2NH_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ .

Another embodiment of this invention pertains to compounds of Formula (I), wherein

$A^1$  is  $N$  or  $C(A^2)$ ;

$A^2$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$B^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$D^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$E^1$  is  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; and

$Y^1$  is  $H$ ,  $CN$ ,  $NO_2$ ,  $C(O)OH$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ ,  $OCF_2CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $C(O)R^{17}$ ,  $C(O)OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ ,  $NH_2$ ,  $NHR^{17}$ ,  $N(R^{17})_2$ ,  $NHC(O)R^{17}$ ,  $C(O)NH_2$ ,  $C(O)NHR^{17}$ ,  $C(O)N(R^{17})_2$ ,  $NHS(O)R^{17}$  or  $NHSO_2R^{17}$ ; or

$E^1$  and  $Y^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$A^2$ ,  $B^1$ , and  $D^1$  are independently selected  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,

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$N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$A^2$ ,  $D^1$ , and  $E^1$  are independently selected  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$A^2$  and  $B^1$ , together with the atoms to which they are attached, are benzene, naphthylene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$D^1$ ,  $E^1$ , and  $Y^1$  are independently selected  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ; or

$A^2$  and  $D^1$ , together with the atoms to which they are attached, are benzene, naphthalene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$B^1$ ,  $E^1$ , and  $Y^1$  are independently selected  $H$ ,  $R^1$ ,  $OR^1$ ,  $SR^1$ ,  $S(O)R^1$ ,  $SO_2R^1$ ,  $C(O)R^1$ ,  $C(O)OR^1$ ,  $OC(O)R^1$ ,  $NHR^1$ ,  $N(R^1)_2$ ,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NH_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(R^1)_2$ ,  $NR^1SO_2NHR^1$ ,  $NR^1SO_2N(R^1)_2$ ,  $C(O)NHNOR^1$ ,  $C(O)NHNOR^1$ ,  $C(O)NHSO_2R^1$ ,  $C(NH)NH_2$ ,  $C(NH)NHR^1$ ,  $C(NH)N(R^1)_2$ ,  $NHSO_2NHR^1$ ,  $NHSO_2N(CH_3)R^1$ ,  $N(CH_3)SO_2N(CH_3)R^1$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CN$ ,  $NO_2$ ,  $N_3$ ,  $OH$ ,  $C(O)H$ ,  $CHNOH$ ,  $CH(NOCH_3)$ ,  $CF_3$ ,  $C(O)OH$ ,  $C(O)NH_2$  or  $C(O)OR^{1,4}$ ;

$G^1$  is  $H$ , or  $C(O)OR$ ;

$R$  is alkyl;

$R^1$  is  $R^2$ ,  $R^3$ ,  $R^4$  or  $R^5$ ;

$R^{1,4}$  is cycloalkyl, cycloalkenyl or cycloalkynyl;

$R^2$  is phenyl, which is unfused or fused with  $R^{2,4}$ ;  $R^{2,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^3$  is heteroaryl, which is unfused or fused with  $R^{3,4}$ ;  $R^{3,4}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;



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R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>4A</sup>; R<sup>4A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>5</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>6</sup>, NC(R<sup>6A</sup>)(R<sup>6B</sup>), R<sup>7</sup>, OR<sup>7</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, C(O)R<sup>7</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>7</sup>, C(O)N(R<sup>7</sup>)<sub>2</sub>, NHC(O)R<sup>7</sup>, NR<sup>7</sup>C(O)R<sup>7</sup>, NHSO<sub>2</sub>R<sup>7</sup>, NHC(O)OR<sup>7</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>7</sup>, SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>7</sup>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NH<sub>2</sub>, NHC(O)CH(CH<sub>3</sub>)NHC(O)CH(CH<sub>3</sub>)NHR<sup>7</sup>, OH, (O), C(O)OH, N<sub>3</sub>, CN, NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>6</sup> is C<sub>2</sub>-C<sub>5</sub>-spiroalkyl, each of which is unsubstituted or substituted with OH, (O), N<sub>3</sub>, CN, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br, I, NH<sub>2</sub>, NH(CH<sub>3</sub>) or N(CH<sub>3</sub>)<sub>2</sub>;

R<sup>6A</sup> and R<sup>6B</sup> are independently selected alkyl or, together with the N to which they are attached, R<sup>6C</sup>;

R<sup>6C</sup> is aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, each having one CH<sub>2</sub> moiety unreplaced or replaced with O, C(O), CNOH, CNOCH<sub>3</sub>, S, S(O), SO<sub>2</sub> or NH;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup>;

R<sup>8</sup> is phenyl, which is unfused or fused with R<sup>8A</sup>; R<sup>8A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>9</sup> is heteroaryl, which is unfused or fused with R<sup>9A</sup>; R<sup>9A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>10A</sup>; R<sup>10A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>11</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup>, SR<sup>12</sup>, S(O)R<sup>12</sup>, SO<sub>2</sub>R<sup>12</sup>, C(O)R<sup>12</sup>, CO(O)R<sup>12</sup>, OC(O)R<sup>12</sup>, OC(O)OR<sup>12</sup>, NH<sub>2</sub>, NHR<sup>12</sup>, N(R<sup>12</sup>)<sub>2</sub>, NHC(O)R<sup>12</sup>, NR<sup>12</sup>C(O)R<sup>12</sup>, NHS(O)<sub>2</sub>R<sup>12</sup>, NR<sup>12</sup>S(O)<sub>2</sub>R<sup>12</sup>, NHC(O)OR<sup>12</sup>, NR<sup>12</sup>C(O)OR<sup>12</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>12</sup>, NHC(O)N(R<sup>12</sup>)<sub>2</sub>, NR<sup>12</sup>C(O)NHR<sup>12</sup>, NR<sup>12</sup>C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>12</sup>, C(O)N(R<sup>12</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>12</sup>, C(O)NHSO<sub>2</sub>R<sup>12</sup>, C(O)NR<sup>12</sup>SO<sub>2</sub>R<sup>12</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>12</sup>, SO<sub>2</sub>N(R<sup>12</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>12</sup>, C(N)N(R<sup>12</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>12</sup> is R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> or R<sup>16</sup>;

R<sup>13</sup> is phenyl, which is unfused or fused with R<sup>13A</sup>; R<sup>13A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>14</sup> is heteroaryl, which is unfused or fused with R<sup>14A</sup>; R<sup>14A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>15</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene, each of which is unfused or fused with R<sup>15A</sup>; R<sup>15A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>16</sup> is alkyl, alkenyl or alkynyl;

R<sup>17</sup> is R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> or R<sup>21</sup>;

R<sup>18</sup> is phenyl, which is unfused or fused with R<sup>18A</sup>; R<sup>18A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>19</sup> is heteroaryl, which is unfused or fused with R<sup>19A</sup>; R<sup>19A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>20</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl each of which is unfused or fused with R<sup>20A</sup>;

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R<sup>20A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>21</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, OR<sup>22</sup>, SR<sup>22</sup>, S(O)R<sup>22</sup>, SO<sub>2</sub>R<sup>22</sup>, C(O)R<sup>22</sup>, CO(O)R<sup>22</sup>, OC(O)R<sup>22</sup>, OC(O)OR<sup>22</sup>, NH<sub>2</sub>, NHR<sup>22</sup>, N(R<sup>22</sup>)<sub>2</sub>, NHC(O)R<sup>22</sup>, NR<sup>22</sup>C(O)R<sup>22</sup>, NHS(O)<sub>2</sub>R<sup>22</sup>, NR<sup>22</sup>S(O)<sub>2</sub>R<sup>22</sup>, NHC(O)OR<sup>22</sup>, NR<sup>22</sup>C(O)OR<sup>22</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>22</sup>, NHC(O)N(R<sup>22</sup>)<sub>2</sub>, NR<sup>22</sup>C(O)NHR<sup>22</sup>, NR<sup>22</sup>C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>22</sup>, C(O)N(R<sup>22</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>22</sup>, C(O)NHSO<sub>2</sub>R<sup>22</sup>, C(O)NR<sup>22</sup>SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>22</sup>, SO<sub>2</sub>N(R<sup>22</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>22</sup>, C(N)N(R<sup>22</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>23</sup>, R<sup>24</sup> or R<sup>25</sup>;

R<sup>23</sup> is phenyl, which is unfused or fused with R<sup>23A</sup>; R<sup>23A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>24</sup> is heteroarene, which is unfused or fused with R<sup>24A</sup>; R<sup>24A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>25</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with R<sup>25A</sup>; R<sup>25A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

Z<sup>1</sup> is R<sup>26</sup> or R<sup>27</sup>;

Z<sup>2</sup> is R<sup>28</sup>, R<sup>29</sup> or R<sup>30</sup>;

Z<sup>1A</sup> and Z<sup>2A</sup> are both absent or are taken together to form CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub> or Z<sup>12A</sup>;

Z<sup>12A</sup> is C<sub>2</sub>-C<sub>6</sub>-alkylene having one or two CH<sub>2</sub> moieties replaced by NH, N(CH<sub>3</sub>), S, S(O) or SO<sub>2</sub>;

L<sup>1</sup> is a R<sup>37</sup>, OR<sup>37</sup>, SR<sup>37</sup>, S(O)R<sup>37</sup>, SO<sub>2</sub>R<sup>37</sup>, C(O)R<sup>37</sup>, CO(O)R<sup>37</sup>, OC(O)R<sup>37</sup>, OC(O)OR<sup>37</sup>, NHR<sup>37</sup>, C(O)NH, C(O)NR<sup>37</sup>, C(O)NHOR<sup>37</sup>, C(O)NHSO<sub>2</sub>R<sup>37</sup>, SO<sub>2</sub>NH, SO<sub>2</sub>NHR<sup>37</sup>, C(N)NH, C(N)NHR<sup>37</sup>;

R<sup>26</sup> is phenylene, which is unfused or fused with R<sup>26A</sup>; R<sup>26A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>27</sup> is heteroarylene, which is unfused or fused with R<sup>27A</sup>; R<sup>27A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>28</sup> is phenylene, which is unfused or fused with R<sup>28A</sup>; R<sup>28A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>29</sup> is heteroarylene, which is unfused or fused with R<sup>29A</sup>; R<sup>29A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>30</sup> is cycloalkylene, cycloalkenylene, heterocycloalkylene or heterocycloalkenylene, each of which is unfused or fused with R<sup>30A</sup>; R<sup>30A</sup> is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>37</sup> is a bond or R<sup>37A</sup>;

R<sup>37A</sup> is alkylene, alkenylene, or alkynylene, each of which is unsubstituted or substituted with one or two or three independently selected R<sup>37B</sup>, OR<sup>37B</sup>, SR<sup>37B</sup>, S(O)R<sup>37B</sup>, SO<sub>2</sub>R<sup>37B</sup>, C(O)R<sup>37B</sup>, CO(O)R<sup>37B</sup>, OC(O)R<sup>37B</sup>, OC(O)OR<sup>37B</sup>, NH<sub>2</sub>, NHR<sup>37B</sup>, N(R<sup>37B</sup>)<sub>2</sub>, NHC(O)R<sup>37B</sup>, NR<sup>37B</sup>C(O)R<sup>37B</sup>, NHS(O)<sub>2</sub>R<sup>37B</sup>, NR<sup>37B</sup>S(O)<sub>2</sub>R<sup>37B</sup>, NHC(O)OR<sup>37B</sup>, NR<sup>37B</sup>C(O)OR<sup>37B</sup>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>37B</sup>, NHC(O)N(R<sup>37B</sup>)<sub>2</sub>, NR<sup>37B</sup>C(O)NHR<sup>37B</sup>, NR<sup>37B</sup>C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHR<sup>37B</sup>, C(O)N(R<sup>37B</sup>)<sub>2</sub>, C(O)NHOH, C(O)NHOR<sup>37B</sup>, C(O)NHSO<sub>2</sub>R<sup>37B</sup>, C(O)NR<sup>37B</sup>SO<sub>2</sub>R<sup>37B</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>37B</sup>, SO<sub>2</sub>N(R<sup>37B</sup>)<sub>2</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>37B</sup>, C(N)N(R<sup>37B</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br and I substituents;

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$R^{37B}$  is alkyl, alkenyl, alkynyl, or  $R^{37C}$ ;  
 $R^{37C}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;  
 $Z^3$  is  $R^{38}$ ,  $R^{39}$  or  $R^{40}$ ;

$R^{38}$  is phenyl, which is unfused or fused with  $R^{38A}$ ;  $R^{38A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{39}$  is heteroaryl, which is unfused or fused with  $R^{39A}$ ;  $R^{39A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{40}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{40A}$ ;  $R^{40A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by  $R^{26}$  and  $R^{27}$  are substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are absent) or further substituted (i.e., if  $Z^{1A}$  and  $Z^{2A}$  are present) with  $R^{41}$ ,  $OR^{41}SR^{41}$ ,  $S(O)R^{41}$ ,  $SO_2R^{41}$ ,  $C(O)R^{41}$ ,  $CO(O)R^{41}$ ,  $OC(O)R^{41}$ ,  $OC(O)OR^{41}$ ,  $NHR^{41}$ ,  $N(R^{41})_2$ ,  $NHC(O)R^{41}$ ,  $NR^{41}C(O)R^{41}$ ,  $NHS(O)_2R^{41}$ ,  $NR^{41}S(O)_2R^{41}$ ,  $NHC(O)OR^{41}$ ,  $NR^{41}C(O)OR^{41}$ ,  $NHC(O)NHR^{41}$ ,  $NHC(O)N(R^{41})_2$ ,  $NR^{41}C(O)NHR^{41}$ ,  $NR^{41}C(O)N(R^{41})_2$ ,  $C(O)NHR^{41}$ ,  $C(O)N(R^{41})_2$ ,  $C(O)NHOH$ ,  $C(O)NHSO_2R^{41}$ ,  $C(O)NR^{41}SO_2R^{41}$ ,  $SO_2NHR^{41}$ ,  $SO_2N(R^{41})_2$ ,  $C(N)NHR^{41}$ , or  $C(N)N(R^{41})_2$ ;

$R^{41}$  is heteroaryl, which is fused with  $R^{43A}$ ;  $R^{43A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; which is fused with benzene, heteroarene or  $R^{43B}$ ;  $R^{43B}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the cyclic moieties represented by  $E^1$  and  $Y^1$  together,  $Y^1$  and  $B^1$  together,  $A^2$  and  $B^1$  together,  $A^2$  and  $D^1$  together,  $R^{1A}$ ,  $R^2$ ,  $R^{2A}$ ,  $R^3$ ,  $R^{3A}$ ,  $R^4$ ,  $R^{4A}$ ,  $R^6$ ,  $R^{6C}$ ,  $R^8$ ,  $R^{8A}$ ,  $R^9$ ,  $R^{9A}$ ,  $R^{10}$ ,  $R^{10A}$ ,  $R^{13}$ ,  $R^{13A}$ ,  $R^{14}$ ,  $R^{14A}$ ,  $R^{15}$ ,  $R^{15A}$ ,  $R^{18}$ ,  $R^{18A}$ ,  $R^{19}$ ,  $R^{19A}$ ,  $R^{20}$ ,  $R^{20A}$ ,  $R^{23}$ ,  $R^{23A}$ ,  $R^{24}$ ,  $R^{24A}$ ,  $R^{25}$ ,  $R^{25A}$ ,  $R^{26}$ ,  $R^{26A}$ ,  $R^{27}$ ,  $R^{27A}$ ,  $R^{28}$ ,  $R^{28A}$ ,  $R^{29}$ ,  $R^{29A}$ ,  $R^{30}$ ,  $R^{30A}$ ,  $R^{37B}$ ,  $R^{38}$ ,  $R^{38A}$ ,  $R^{39}$ ,  $R^{39A}$ ,  $R^{40}$ , and  $R^{40A}$  are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SR^{57}$ ,  $S(O)R^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $OC(O)R^{57}$ ,  $OC(O)OR^{57}$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NR^{57}C(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $NR^{57}S(O)_2R^{57}$ ,  $NHC(O)OR^{57}$ ,  $NR^{57}C(O)OR^{57}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{57}$ ,  $NHC(O)N(R^{57})_2$ ,  $NR^{57}C(O)NHR^{57}$ ,  $NR^{57}C(O)N(R^{57})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{57}$ ,  $C(O)N(R^{57})_2$ ,  $C(O)NHOH$ ,  $C(O)NHSO_2R^{57}$ ,  $C(O)NR^{57}SO_2R^{57}$ ,  $SO_2NHR^{57}$ ,  $SO_2N(R^{57})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{57}$ ,  $C(N)N(R^{57})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl, which is unfused or fused with  $R^{58A}$ ;  $R^{58A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{59}$  is heteroaryl, which is unfused or fused with  $R^{59A}$ ;  $R^{59A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{60}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{60A}$ ;  $R^{60A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{61}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $SR^{62}$ ,  $S(O)R^{62}$ ,  $SO_2R^{62}$ ,  $COR^{62}$ ,  $CO(O)R^{62}$ ,  $OC(O)R^{62}$ ,  $OC(O)OR^{62}$ ,  $NH_2$ ,  $NHR^{62}$ ,  $N(R^{62})_2$ ,  $NHC(O)R^{62}$ ,  $NR^{62}C(O)R^{62}$ ,  $NHS(O)_2R^{62}$ ,  $NR^{62}S(O)_2R^{62}$ ,  $NHC(O)OR^{62}$ ,  $NR^{62}C(O)OR^{62}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{62}$ ,

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$NHC(O)N(R^{62})_2$ ,  $NR^{62}C(O)NHR^{62}$ ,  $NR^{62}C(O)N(R^{62})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{62}$ ,  $C(O)N(R^{62})_2$ ,  $C(O)NHOH$ ,  $C(O)NHSO_2R^{62}$ ,  $C(O)NR^{62}SO_2R^{62}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{62}$ ,  $SO_2N(R^{62})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{62}$ ,  $C(N)N(R^{62})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{62}$  is  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$  or  $R^{66}$ ;

$R^{63}$  is phenyl, which is unfused or fused with  $R^{63A}$ ;  $R^{63A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{64}$  is heteroaryl, which is unfused or fused with  $R^{64A}$ ;  $R^{64A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{65}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, each of which is unfused or fused with  $R^{65A}$ ;  $R^{65A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{66}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{67}$ ,  $OR^{67}$ ,  $SR^{67}$ ,  $S(O)R^{67}$ ,  $SO_2R^{67}$ ,  $C(O)R^{67}$ ,  $CO(O)R^{67}$ ,  $OC(O)R^{67}$ ,  $OC(O)OR^{67}$ ,  $NH_2$ ,  $NHR^{67}$ ,  $N(R^{67})_2$ ,  $NHC(O)R^{67}$ ,  $NR^{67}C(O)R^{67}$ ,  $NHS(O)_2R^{67}$ ,  $NR^{67}S(O)_2R^{67}$ ,  $NHC(O)OR^{67}$ ,  $NR^{67}C(O)OR^{67}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{67}$ ,  $NHC(O)N(R^{67})_2$ ,  $NR^{67}C(O)NHR^{67}$ ,  $NR^{67}C(O)N(R^{67})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{67}$ ,  $C(O)N(R^{67})_2$ ,  $C(O)NHOH$ ,  $C(O)NHSO_2R^{67}$ ,  $C(O)NR^{67}SO_2R^{67}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{67}$ ,  $SO_2N(R^{67})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{67}$ ,  $C(N)N(R^{67})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$  substituents;

$R^{67}$  is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$ ,  $R^{63}$ ,  $R^{64}$ ,  $R^{65}$ , and  $R^{67}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $OR^{68}$ ,  $SR^{68}$ ,  $S(O)R^{68}$ ,  $SO_2R^{68}$ ,  $C(O)R^{68}$ ,  $CO(O)R^{68}$ ,  $OC(O)R^{68}$ ,  $OC(O)OR^{68}$ ,  $NH_2$ ,  $NHR^{68}$ ,  $N(R^{68})_2$ ,  $NHC(O)R^{68}$ ,  $NR^{68}C(O)R^{68}$ ,  $NHS(O)_2R^{68}$ ,  $NR^{68}S(O)_2R^{68}$ ,  $NHC(O)OR^{68}$ ,  $NR^{68}C(O)OR^{68}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{68}$ ,  $NHC(O)N(R^{68})_2$ ,  $NR^{68}C(O)NHR^{68}$ ,  $NR^{68}C(O)N(R^{68})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{68}$ ,  $C(O)N(R^{68})_2$ ,  $C(O)NHOH$ ,  $C(O)NHSO_2R^{68}$ ,  $C(O)NR^{68}SO_2R^{68}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{68}$ ,  $SO_2N(R^{68})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{68}$ ,  $C(N)N(R^{68})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{68}$  is  $R^{69}$ ,  $R^{70}$ ,  $R^{71}$  or  $R^{72}$ ;

$R^{69}$  is phenyl, which is unfused or fused with  $R^{69A}$ ;  $R^{69A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{70}$  is heteroaryl, which is unfused or fused with  $R^{70A}$ ;  $R^{70A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{71}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with  $R^{71A}$ ;  $R^{71A}$  is benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{72}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{73}$ ,  $OR^{73}$ ,  $SR^{73}$ ,  $S(O)R^{73}$ ,  $SO_2R^{73}$ ,  $C(O)R^{73}$ ,  $CO(O)R^{73}$ ,  $OC(O)R^{73}$ ,  $OC(O)OR^{73}$ ,  $NH_2$ ,  $NHR^{73}$ ,  $N(R^{73})_2$ ,  $NHC(O)R^{73}$ ,  $NR^{73}C(O)R^{73}$ ,  $NHS(O)_2R^{73}$ ,  $NR^{73}S(O)_2R^{73}$ ,  $NHC(O)OR^{73}$ ,  $NR^{73}C(O)OR^{73}$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{73}$ ,  $NHC(O)N(R^{73})_2$ ,  $NR^{73}C(O)NHR^{73}$ ,  $NR^{73}C(O)N(R^{73})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{73}$ ,  $C(O)N(R^{73})_2$ ,  $C(O)NHOH$ ,  $C(O)NHSO_2R^{73}$ ,  $C(O)NR^{73}SO_2R^{73}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{73}$ ,  $SO_2N(R^{73})_2$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{73}$ ,  $C(N)N(R^{73})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $CN$ ,  $N_3$ ,  $NO_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

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NH<sub>2</sub>, C(N)NHR<sup>73</sup>, C(N)N(R<sup>73</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

R<sup>73</sup> is alkyl, alkenyl, alkynyl, phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; and

wherein the moieties represented by R<sup>69</sup>, R<sup>70</sup>, and R<sup>71</sup> are unsubstituted or substituted with one or two or three or four of independently selected NH<sub>2</sub>, C(O)NH<sub>2</sub>, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, C(O)H, C(O)OH, C(N)NH<sub>2</sub>, OH, (O), CN, N<sub>3</sub>, NO<sub>2</sub>, CF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I.

In one embodiment of Formula (I), A<sup>1</sup> is N, and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>) and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H, F, Cl, Br, or I; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and G<sup>1</sup> is H.

In one embodiment of Formula (I), B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>, and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>, and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; and G<sup>1</sup> is H.

In one embodiment of Formula (I), D<sup>1</sup> is H or Cl. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and G<sup>1</sup> is H.

In one embodiment of Formula (I), E<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; D<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; D<sup>1</sup> is Cl; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and G<sup>1</sup> is H.

In one embodiment of Formula (I), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (I), Y<sup>1</sup> is H. In another embodiment of Formula (I), Y<sup>1</sup> is CN. In another embodiment of Formula (I), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (I),

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Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (I), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (I), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (I), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (I), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (I), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (I), Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (I), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; G<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); and A<sup>2</sup> is H. In another embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (I), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>.

In one embodiment of Formula (I), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (I), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (I), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (I), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of



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Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is substituted with  $N(R^{57})_2$ . In another embodiment of Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $N(R^{57})_2$ . In another embodiment of Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $N(R^{57})_2$ ;  $R^{57}$  is  $R^{61}$ ; and  $R^{61}$  is alkyl which is unsubstituted or substituted with  $R^{62}$ . In another embodiment of Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{61}$ ; and  $R^{61}$  is alkyl which is unsubstituted or substituted with  $R^{62}$ ;  $R^{62}$  is  $R^{65}$ ; and  $R^{65}$  is cycloalkyl. In another embodiment of Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{61}$ ; and  $R^{61}$  is alkyl which is substituted with  $R^{62}$ ;  $R^{62}$  is  $R^{65}$ ; and  $R^{65}$  is cyclopropyl.

In one embodiment of Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl; wherein  $R^4$  is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with  $R^{57}$ . In another embodiment of Formula (I),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the heterocycloalkyl ring is substituted with  $R^{57}$ ; and  $R^{57}$  is  $R^{60}$  or  $R^{61}$ . In another embodiment of Formula (I),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{60}$  or  $R^{61}$ ;  $R^{60}$  is heterocycloalkyl; and  $R^{61}$  is alkyl. In another embodiment of Formula (I),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{60}$ ;  $R^{60}$  is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (I),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{61}$ ;  $R^{61}$  is alkyl; and the alkyl is methyl. In another embodiment of Formula (I),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with  $C(O)OR^{57}$ ;  $R^{57}$  is  $R^{61}$ ;  $R^{61}$  is alkyl; and the alkyl is methyl.

In one embodiment of Formula (I),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is unsubstituted or substituted. In one embodiment of Formula (I),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is unsubstituted or substituted with  $R^7$ ,  $OR^7$ ,  $OH$ ,  $CN$ , or  $F$ . In another embodiment of Formula (I),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is substituted with  $R^7$ ,  $OR^7$ ,  $NHR^7$ , or  $N(R^7)_2$ .

In one embodiment of Formula (I),  $R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$  or  $R^{11}$  which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^7$  is  $R^8$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^7$  is  $R^9$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^7$  is  $R^{10}$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^7$  is  $R^{11}$  which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (I),  $R^8$  is phenyl which is unsubstituted or substituted as defined herein.

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In one embodiment of Formula (I),  $R^9$  is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^9$  is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^9$  is furanyl; which is unsubstituted.

In one embodiment of Formula (I),  $R^{10}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{10}$  is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{10}$  is tetrahydropyranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{10}$  is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{10}$  is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{10}$  is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{10}$  is heterocycloalkyl which is fused with  $R^{10A}$ ; and  $R^{10A}$  is heteroarene. In another embodiment of Formula (I),  $R^{10}$  is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (I),  $R^{11}$  is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{11}$  is alkyl. In another embodiment of Formula (I),  $R^{11}$  is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (I),  $R^{11}$  is alkyl; which is substituted as defined herein. In another embodiment of Formula (I),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ,  $OR^{12}$ , or  $CF_3$ . In another embodiment of Formula (I),  $R^{11}$  is alkyl; which is substituted with  $OR^{12}$ ,  $R^{12}$  is  $R^{16}$ ; and  $R^{16}$  is alkyl. In another embodiment of Formula (I),  $R^{11}$  is alkyl; which is substituted with  $CF_3$ . In another embodiment of Formula (I),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ;  $R^{12}$  is  $R^{14}$ ; and  $R^{14}$  is heteroaryl.

In one embodiment of Formula (I),  $A^1$  is  $N$  or  $C(A^2)$ ;

$A^2$  is  $H$ ,  $F$ ,  $Br$ ,  $I$ , or  $Cl$ ;

$B^1$  is  $R^1$ ,  $OR^1$ ,  $NHR^1$ ,  $NHC(O)R^1$ ,  $F$ ,  $Br$ ,  $I$  or  $Cl$ ;

$D^1$  is  $H$ ,  $F$ ,  $Br$ ,  $I$ , or  $Cl$ ;

$E^1$  is  $H$ ; and

$Y^1$  is  $H$ ,  $CN$ ,  $NO_2$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ , or  $C(O)NH_2$ ; or

$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and  $A^2$ ,  $D^1$ , and  $E^1$  are independently selected  $H$ ;

$G^1$  is  $H$ , or  $C(O)OR$ ;

$R$  is alkyl;

$R^1$  is  $R^4$  or  $R^5$ ;

$R^4$  is cycloalkyl, or heterocycloalkyl;

$R^5$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^7$ ,  $OR^7$ ,  $NHR^7$ ,  $N(R^7)_2$ ,  $CN$ ,  $OH$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$ , or  $R^{11}$ ;

$R^8$  is phenyl;

$R^9$  is heteroaryl;

$R^{10}$  is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with  $R^{10A}$ ;  $R^{10A}$  is heteroarene;

$R^{11}$  is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{12}$ ,  $OR^{12}$  or  $CF_3$ ;



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$R^{12}$  is  $R^{14}$  or  $R^{16}$ ;  
 $R^{14}$  is heteroaryl;  
 $R^{16}$  is alkyl;  
 $R^{17}$  is  $R^{21}$ ;  
 $R^{21}$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{22}$ , F, Cl, Br or I;  
 $R^{22}$  is  $R^{25}$ ;  
 $R^{25}$  is heterocycloalkyl;  
 $Z^1$  is  $R^{26}$ ;  
 $Z^2$  is  $R^{30}$ ;  
 $Z^{1,4}$  and  $Z^{2,4}$  are both absent;  
 $L^1$  is a  $R^{37}$ ;  
 $R^{26}$  is phenylene;  
 $R^{30}$  is heterocycloalkylene;  
 $R^{37}$  is  $R^{37A}$ ;  
 $R^{37A}$  is alkylene;  
 $Z^3$  is  $R^{38}$ , or  $R^{40}$ ;  
 $R^{38}$  is phenyl;  
 $R^{40}$  is cycloalkyl, cycloalkenyl, or heterocycloalkenyl;  
 wherein the moiety represented by  $R^{26}$  is substituted with  $OR^{41}$ ;  
 $R^{41}$  is heteroaryl, which is fused with  $R^{43A}$ ;  $R^{43A}$  is heteroarene; which is unfused or fused with benzene;  
 wherein the cyclic moieties represented by  $Y^1$  and  $B^1$  together,  $R^4$ ,  $R^8$ ,  $R^{10}$ ,  $R^{25}$ ,  $R^{30}$ ,  $R^{38}$ , and  $R^{40}$  are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $C(O)N(R^{57})_2$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $OH$ ,  $CN$ ,  $(O)$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;  
 $R^{57A}$  is spiroalkyl, or spiroheteroalkyl;  
 $R^{57}$  is  $R^{58}$ ,  $R^{59}$ ,  $R^{60}$  or  $R^{61}$ ;  
 $R^{58}$  is phenyl;  
 $R^{59}$  is heteroaryl;  
 $R^{60}$  is cycloalkyl, or heterocycloalkyl;  
 $R^{61}$  is alkyl which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $N(R^{62})_2$ ,  $C(O)OH$ ,  $CN$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;  
 $R^{62}$  is  $R^{65}$  or  $R^{66}$ ;  
 $R^{65}$  is cycloalkyl, or heterocycloalkyl;  
 $R^{66}$  is alkyl which is unsubstituted or substituted with  $OR^{67}$ ;  
 $R^{67}$  is alkyl;  
 wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ , and  $R^{60}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;  
 $R^{68}$  is  $R^{71}$  or  $R^{72}$ ;  
 $R^{71}$  is heterocycloalkyl; and  
 $R^{72}$  is alkyl, which is unsubstituted or substituted with one or two F.

Still another embodiment pertains to compounds having Formula (I), which are

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-{4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl}-N-{3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide;  
2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl}sulfonyl)benzamide;  
Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[[3(S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[[3(R)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]

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pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;

N-({5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-acetyl)piperidin-4-yl]amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-{[2-(2-methoxyethoxy)ethyl}sulfonyl}phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[2-(2-methoxyethoxy)

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ethyl)sulfonyl]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-({[4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl)amino]-3-nitrophenyl}sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-oxo-3,4-dihydroquinazolin-6-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 3-({4-({4-({[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}amino)sulfonyl)-2-nitrophenoxymethylmorpholine-4-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-chloro-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts, and metabolites thereof.

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-(2,2-difluoroethyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-morpholin-4-ylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-(dicyclopropyl)



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lamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-({[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[4-morpholin-4-ylcyclohexyl]amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({4-(cyclopropylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-([4-({[4-({[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl)-4-fluoropiperidine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([4-(tetrahydro-2H-pyran-4-ylpiperazin-1-yl)cyclohexyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl}methoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3S)-1-tetrahydro-2H-pyran-4-yl]azetidin-3-yl}amino)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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dro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(4-{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclobutylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino]phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-[(4-{[(1-acetyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-(2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 20 N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 25 N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 40 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 45 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 50 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(2-fluoro-1-(fluoromethyl)ethyl)azetidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 55 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 60 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropylpiperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 65 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropylpiperidin-

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4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2,2-difluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4,4-difluoro-1-oxetan-3-yl]pyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(4-cyclobutylmorpholin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[4-(tetrahydrofuran-3-yl)morpholin-3-yl]methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(cyclopropyl-4-fluoropiperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(4-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[3-methoxybenzyl]amino)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-{[4-({[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-({[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-({[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-({[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(3-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-({[3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-({[cis-3-morpholin-4-ylcyclopentyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-({4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(3-(dimethylamino)propoxy]benzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(2-morpholin-4-ylethoxy)benzyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[1-methyl-5-oxopyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5R,6S)-5,6-dihydrobicyclo[2.2.1]hept-2-yl]methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5S,6R)-5,6-dihydrobicyclo[2.2.1]hept-2-yl]methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-([4-({[3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-({[4-fluorotetrahydro-2H-pyran-4-yl]methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-({[2-(2-methoxyethoxy)ethyl]morpholin-2-yl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(cyanomethyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

(2-{[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]methyl)morpholin-4-yl)acetic acid;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(cyclopropyl)morpholin-2-yl]methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-({[1-tert-butylpiperidin-4-yl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[1-(2-methoxyethyl)piperidin-3-yl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-fluoro-1-methylpiperidin-4-yl]methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-([4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl)-2-nitrophenyl)amino]piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-(pentafluoro- $\lambda^6$ -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-methoxytetrahydro-2H-pyran-4-yl]methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-((3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([4-(oxetan-3-yl)piperazin-1-yl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(4-difluorocyclohexyl)methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([4-([1-tert-butylpiperidin-4-yl]amino)-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-([4-(oxetan-3-yl)morpholin-2-yl]methyl]amino)-3-[(trifluoromethyl)sulfonyl]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxyl]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophe-

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nyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-([5-chloro-6-([3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-([3-difluoropropan-2-yl)morpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-([1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-((3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-((3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([1-(oxetan-3-yl)azetidin-3-yl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-([1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-([2-((2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-([2-((2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-([1-(N,N-dimethylglycyl)piperidin-4-yl]methoxyl]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl)methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]-3-(trifluoromethyl)phenyl)sulfonyl]benzamide;

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-cyanocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 N-[(5-chloro-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-(3-furylmethoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

15 N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

25 N-[(5-chloro-6-[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 N-[(5-chloro-6-[(1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

35 N-[(3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-(tetrahydro-2H-pyran-4-yl)methoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

40 N-[(5-chloro-6-[(1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl)methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

45 N-[(3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

50 N-[(5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-[(1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

55 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

60 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

65 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)

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propyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)benzamide;  
 N-([5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(4-fluorotetrahydro-2H-pyran-4-ylmethoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-{[1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(3-[cyclopropyl(oxetan-3-yl)amino]propyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-[(2S)-4-cyclopropylmorpholin-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-([3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 methyl 2-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)amino]methyl]morpholine-4-carboxylate;  
 2-([4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(4-(methylsulfonyl)morpholin-2-yl]methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(3-[cyclobutyl(cyclopropyl)amino]propyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(trans-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxymorpholin-2-yl]methyl]amino}-3-nitrophenyl]sulfonyl}-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-{[4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-{[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-{[(2-chloro-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

(2S)-2-{[(3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

N-{[5-chloro-6-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-{[(3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)amino]methyl}-N-ethyl-N-methylmorpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(cis-4-hydroxy-4-methyl-

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ylcyclohexyl)methyl]amino}-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{(trans-4-hydroxy-4-methylcyclohexyl)methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{(trans-4-hydroxy-4-methylcyclohexyl)methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{(cis-4-hydroxy-4-methylcyclohexyl)methoxypyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(2,2-difluorocyclopropyl)amino]cyclohexyl]amino}-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{(cis-1-fluoro-4-hydroxycyclohexyl)methoxypyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-{(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-cyclopropylmorpho-



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lin-2-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl)methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl}amino)methyl pivalate;

{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl}amino)methyl butyrate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({[3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl})benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

10 N-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfonyl}-2-nitrophenyl)morpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxymethyl)cyclohexyl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

25 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

30 Still another embodiment pertains to 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

35 Still another embodiment pertains to Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

40 Still another embodiment pertains to Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

45 Still another embodiment pertains to Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

50 Still another embodiment pertains to Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

55 Still another embodiment pertains to Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

60 Another embodiment pertains to the compound N-[(5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-



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yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}(<sup>2</sup>H<sub>8</sub>)piperazin-1-yl]-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-((5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-cyclopropyl(oxetan-3-yl)amino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-cyclopropyl(oxetan-3-yl)amino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-cyclopropyl(oxetan-3-yl)amino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

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Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-cyclopropyl(oxetan-3-yl)amino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxan-2-yl)methoxy]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino)pyridin-3-yl]sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino)-3-nitrophenyl]sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-cyclopropyl(oxetan-

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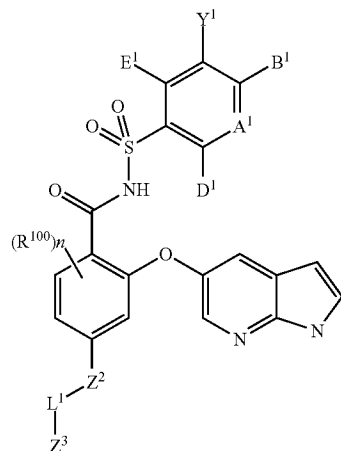
3-yl)amino]propyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-({[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound N-[(5-chloro-6-[[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Still another embodiment pertains to compounds having Formula (I) or Formula (II), which are N-[(4-{{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; or a pharmaceutically acceptable salt thereof.

Another embodiment pertains to the compound 4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides compounds of Formula (II)



and therapeutically acceptable salts, and metabolites thereof, wherein A<sup>1</sup>, B<sup>1</sup>, D<sup>1</sup>, E<sup>1</sup>, Y<sup>1</sup>, Z<sup>2</sup>, L<sup>1</sup>, and Z<sup>3</sup> are as described herein for Formula (II); n is 0, 1, 2, or 3; describing the number of substituents on Z<sup>1</sup>; and R<sup>100</sup> is as described for substituents on R<sup>26</sup>.

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In one embodiment of Formula (II), n is 0 or 1. In another embodiment of Formula (II), n is 0.

In one embodiment of Formula (II), A<sup>1</sup> is N. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>). In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); and A<sup>2</sup> is H, F, Cl, Br, or I. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); and A<sup>2</sup> is H.

In one embodiment of Formula (II), B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is Cl. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is R<sup>1</sup>. In another embodiment of Formula (II), A<sup>1</sup> is N; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (II), A<sup>1</sup> is N; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (II), A<sup>1</sup> is N; and B<sup>1</sup> is Cl. In another embodiment of Formula (II), A<sup>1</sup> is N; and B<sup>1</sup> is R<sup>1</sup>.

In one embodiment of Formula (II), D<sup>1</sup> is H or Cl. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H.

In one embodiment of Formula (II), E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

In one embodiment of Formula (II), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (II), Y<sup>1</sup> is H. In another embodiment of Formula (II), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (II), Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (II), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (II), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (II), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (II), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (II), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (II), Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In

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another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (II), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); and A<sup>2</sup> is H. In another embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (II), G<sup>1</sup> is H; A<sup>1</sup> is N or C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>.

In one embodiment of Formula (II), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (II), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (II), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another

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embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is tetrahydropyranyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R is alkyl; and the alk R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is methyl. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.

In one embodiment of Formula (II), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted. In one embodiment of Formula (II), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted with R<sup>7</sup>, OR<sup>7</sup>, OH, CN, or F. In another embodiment of Formula (II), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is substituted with R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, or N(R<sup>7</sup>)<sub>2</sub>.

In one embodiment of Formula (II), R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup> which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>7</sup> is R<sup>8</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>7</sup> is R<sup>9</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>7</sup> is R<sup>10</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>7</sup> is R<sup>11</sup> which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (II), R<sup>8</sup> is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (II), R<sup>9</sup> is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>9</sup> is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>9</sup> is furanyl; which is unsubstituted.

In one embodiment of Formula (II), R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>10</sup> is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>10</sup> is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>10</sup> is tetrahydropyranyl, which is unsubstituted or substituted as defined herein. In another embodiment



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of Formula (II), R<sup>10</sup> is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>10</sup> is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptan-1-yl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>10</sup> is heterocycloalkyl which is fused with R<sup>10A</sup>; and R<sup>10A</sup> is heteroarene. In another embodiment of Formula (II), R<sup>10</sup> is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (II), R<sup>11</sup> is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>11</sup> is alkyl. In another embodiment of Formula (II), R<sup>11</sup> is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (II), R<sup>11</sup> is alkyl; which is substituted as defined herein. In another embodiment of Formula (II), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>, OR<sup>12</sup>, or CF<sub>3</sub>. In another embodiment of Formula (II), R<sup>11</sup> is alkyl; which is substituted with OR<sup>12</sup>; R<sup>12</sup> is R<sup>16</sup>; and R<sup>16</sup> is alkyl. In another embodiment of Formula (II), R<sup>11</sup> is alkyl; which is substituted with CF<sub>3</sub>. In another embodiment of Formula (II), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>, R<sup>12</sup> is R<sup>14</sup>, and R<sup>14</sup> is heteroaryl.

In one embodiment of Formula (II),  
n is 0;  
A<sup>1</sup> is N or C(A<sup>2</sup>);  
A<sup>2</sup> is H, F, Br, I, or Cl;  
B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Br, I or Cl;  
D<sup>1</sup> is H, F, Br, I, or Cl;  
E<sup>1</sup> is H; and  
Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>; or  
Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and  
A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H;  
R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>;  
R<sup>4</sup> is cycloalkyl, or heterocycloalkyl;  
R<sup>5</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, CN, OH, F, Cl, Br or I;  
R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, or R<sup>11</sup>;  
R<sup>8</sup> is phenyl;  
R<sup>9</sup> is heteroaryl;  
R<sup>10</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R<sup>10A</sup>; R<sup>10A</sup> is heteroarene;  
R<sup>11</sup> is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup> or CF<sub>3</sub>;  
R<sup>12</sup> is R<sup>14</sup> or R<sup>16</sup>;  
R<sup>14</sup> is heteroaryl;  
R<sup>16</sup> is alkyl;  
R<sup>17</sup> is R<sup>21</sup>;  
R<sup>21</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, F, Cl, Br or I;  
R<sup>22</sup> is R<sup>25</sup>;  
R<sup>25</sup> is heterocycloalkyl;  
Z<sup>2</sup> is R<sup>30</sup>;  
Z<sup>1A</sup> and Z<sup>2A</sup> are both absent;  
L<sup>1</sup> is a R<sup>37</sup>;  
R<sup>30</sup> is heterocycloalkylene;  
R<sup>37</sup> is R<sup>37A</sup>;  
R<sup>37A</sup> is alkylene;  
Z<sup>3</sup> is R<sup>38</sup>, or R<sup>40</sup>;  
R<sup>38</sup> is phenyl;  
R<sup>40</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkenyl;

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wherein the cyclic moieties represented by Y<sup>1</sup> and B<sup>1</sup> together, R<sup>4</sup>, R<sup>8</sup>, R<sup>10</sup>, R<sup>25</sup>, R<sup>30</sup>, R<sup>38</sup>, and R<sup>40</sup> are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NHS(O)<sub>2</sub>R<sup>57</sup>, OH, CN, (O), F, Cl, Br or I;

R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;  
R<sup>57</sup> is R<sup>58</sup>, R<sup>60</sup> or R<sup>61</sup>;  
R<sup>58</sup> is phenyl;  
R<sup>60</sup> is cycloalkyl, or heterocycloalkyl;  
R<sup>61</sup> is alkyl which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, C(O)OH, CN, F, Cl, Br or I; R<sup>62</sup> is R<sup>65</sup>, or R<sup>66</sup>;  
R<sup>65</sup> is cycloalkyl, or heterocycloalkyl;  
R<sup>66</sup> is alkyl which is unsubstituted or substituted with OR<sup>67</sup>;  
R<sup>67</sup> is alkyl;

wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, and R<sup>60</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, F, Cl, Br or I;  
R<sup>68</sup> is R<sup>71</sup> or R<sup>72</sup>;  
R<sup>71</sup> is heterocycloalkyl; and  
R<sup>72</sup> is alkyl, which is unsubstituted or substituted with one or two F.

Still another embodiment pertains to compounds having Formula (II), which are 4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
Trans-4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(4-morpholin-4-yl)cyclohexyl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-{4-[(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl}-N-({4-[(1,4-dioxan-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{(tetrahydro-2H-pyran-4-ylmethyl)amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[(4-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-morpholin-4-ylcyclohexyl)amino]-3-(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)amino]-3-(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5-[(4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;

N-[(5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2,2-dimethyltetrahydro-

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2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({4-[(1-acetyl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl})-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([2-(2-methoxyethoxy)ethyl]sulfonyl)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-N-([4-({4-[(bis(cyclopropylmethyl)amino]cyclohexyl)amino]-3-nitrophenyl)sulfonyl)-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(methylpiperidin-4-yl)methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl})-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-oxo-3,4-dihydroquinazolin-6-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-([4-([4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-([4-([4-methoxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl})-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 tert-butyl 3-([4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl)-2-nitrophenoxymethylmorpholine-4-carboxylate;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-3-ylmethoxy)-3-nitrophenyl]sulfonyl})-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(methylsulfonyl)piperidin-4-yl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([4-chloro-3-nitrophenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-

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2H-pyran-4-yl)piperidin-4-yl]oxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 and therapeutically acceptable salts, and metabolites thereof.  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-(2,2-difluoroethyl)piperidin-4-yl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-(1-morpholin-4-ylcyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-(dicyclopropylamino)cyclohexyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-{[4-[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino]-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 10 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 15 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 20 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 25 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(1-cis-3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 40 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 45 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;  
 50 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide;  
 55 Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(4-cyclopropylamino)cyclohexyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 60 Trans-N-({5-bromo-6-[(4-morpholin-4-yl)cyclohexyl]oxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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Trans-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-{{[4-({[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-nitrophenoxymethyl]-4-fluoropiperidine-1-carboxylate;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cyclohexyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({[1-2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(4-acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclobutylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{3-nitro-4-{{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl}amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({[1-(methylsulfonyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(1-acetyl)piperidin-3-yl]methyl}amino}-3-nitrophenyl)sulfonyl]-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({[1-2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{{4-({[1-(methylsulfonyl)pyrrolidin-3-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl}sulfonyl)-4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1R,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[1-(2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1-cyclopropyl)piperidin-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(2-fluoroethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluoro-1-oxetan-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclobutyl)morpholin-3-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydrofuran-3-yl)morpholin-3-yl]methyl}amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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ethyl)ethyl]piperidin-4-yl]methyl]amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxybenzyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3-trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-methoxybenzyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-difluoromethoxy)benzyl]amino}-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-[(4-{[(4-(acetylamino)cyclohexyl]amino)-3-nitrophenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxybenzyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-hydroxybenzyl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-3-morpholin-4-yl)cyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{4-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-[3-(dimethylamino)propoxy]benzyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-(2-morpholin-4-ylethoxy)benzyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(E)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(Z)-4-hydroxy-1-adamantyl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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droxybicyclo[2.2.1]hept-2-yl]methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-(cyanomethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

(2-{[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benoyl]sulfamoyl}-2-nitrophenyl)amino]methyl}morpholin-4-yl)acetic acid;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-({4-[(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[(4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-

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pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

ethyl 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]-2-nitrophenyl)amino]piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro- $\lambda^6$ -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-tetrahydrofuran-3-ylamino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(1,3-difluoropropan-



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2-yl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[3-nitro-4-[[1-(oxetan-3-yl)azetidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((2R)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((2S)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-((3R)-1-(cyanomethyl)pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-[[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 5 N-((5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 10 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-((3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-((5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 20 4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-((4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)-3-(trifluoromethyl)phenyl)sulfonyl)benzamide;  
 25 N-[(5-chloro-6-[[1-(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 30 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((3-nitro-4-[(trans-4-cyanocyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 35 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((4-[(trans-4-cyanocyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 40 N-[(5-chloro-6-[[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-((5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[[4-(3-furylmethoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 50 N-[(5-chloro-6-[[1-(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 55 N-[(5-chloro-6-[[1-(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 60 N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-((3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-



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dimethylcyclohex-1-en-1-yl)methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-[(5-chloro-6-([1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-([1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropylamino)propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(methoxyacetyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-([6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)benzamide;  
 N-([5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-cyano-4-[(4-fluorotetrahy-

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dro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([trans-4-(morpholin-4-yl)cyclohexyl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(2,2,2-trifluoroethyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(oxetan-3-yl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-(cyclopropyl(oxetan-3-yl)amino]propyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([3-chloro-4-([1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy)phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-([5-chloro-6-([2S)-4-cyclopropylmorpholin-2-yl]methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-

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pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-{[3-chloro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

methyl 2-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]methyl]morpholine-4-carboxylate;

2-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3-cyclobutyl(cyclopropyl)amino]propyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(trans-4-hydroxycyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-{[4-fluorotetrahydro-2H-pyran-4-yl]methoxy}phenyl]sulfonyl}-4-(4-{[9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{[4-cyclopropyl(oxetan-3-yl)amino]cyclohexyl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-{[4-[(4-cyclopropylmorpholin-2-yl)amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-{[4-cyclopropylmorpholin-2-yl]methoxy}phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimeth-

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ylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[3-chloro-4-{[4-cyclopropylmorpholin-2-yl]methyl]amino}phenyl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-[[2-chloro-4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

(2S)-2-[[3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl]oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

N-{[5-chloro-6-{[4-cyclopropylmorpholin-2-yl]methyl]amino}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-[[3-chloro-5-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(4-{[2-(cyanoethyl)(cyclopropyl)amino]cyclohexyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide};

N-{[5-chloro-6-{(trans-4-hydroxy-4-methylcyclohexyl)methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{[5-chloro-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl]sulfonyl}-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-[(4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2S)-4-(oxetan-

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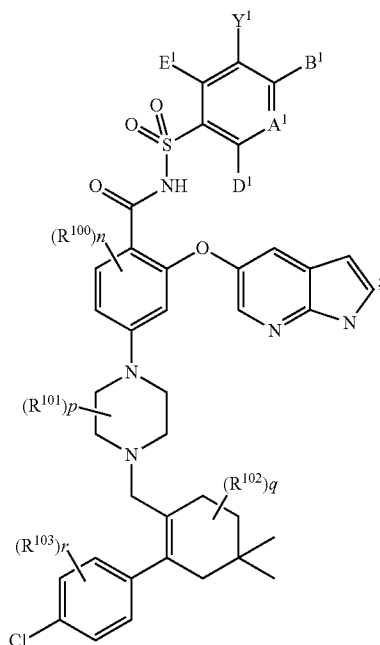
3-yl)morpholin-2-yl]methyl}amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-({3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl)methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({3-(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl}sulfonyl)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 N-4-({4-4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl)-2-nitrophenyl)morpholine-4-carboxamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(methoxymethyl)cyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[(1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.



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In another aspect, the present invention provides compounds of Formula (III)



and therapeutically acceptable salts, and metabolites thereof, wherein  $A^1$ ,  $B^1$ ,  $D^1$ ,  $E^1$ , and  $Y^1$  are as described herein for Formula (I);  $R^{100}$  is as described for substituents on  $R^{26}$ ;  $n$  is 0, 1, 2, or 3;  $R^{101}$  is as described for substituents on  $R^{30}$ ;  $p$  is 0, 1, 2, 3, 4, 5, or 6;  $R^{102}$  is as described for substituents on  $R^{40}$ ;  $q$  is 0, 1, 2, 3, 4, 5, or 6;  $R^{103}$  is as described for substituents on  $R^{58}$ ; and  $r$  is 0, 1, 2, 3, or 4.

In one embodiment of Formula (III),  $n$ ,  $p$ ,  $r$ , and  $q$  are each 0.

In one embodiment of Formula (III),  $A^1$  is N. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ . In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ; and  $A^2$  is H, F, Cl, Br, or I. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ; and  $A^2$  is H.

In one embodiment of Formula (III),  $B^1$  is  $R^1$ , OR<sup>1</sup>, %NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H; and  $B^1$  is NHR<sup>1</sup>. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H; and  $B^1$  is OR<sup>1</sup>. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H; and  $B^1$  is Cl. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H; and  $B^1$  is  $R^1$ . In another embodiment of Formula (III),  $A^1$  is N; and  $B^1$  is NHR<sup>1</sup>. In another embodiment of Formula (III),  $A^1$  is N; and  $B^1$  is OR<sup>1</sup>. In another embodiment of Formula (III),  $A^1$  is N; and  $B^1$  is Cl. In another embodiment of Formula (III),  $A^1$  is N; and  $B^1$  is  $R^1$ .

In one embodiment of Formula (III),  $D^1$  is H or Cl. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is NHR<sup>1</sup>; and  $D^1$  is H. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is NHR<sup>1</sup>; and  $D^1$  is Cl. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is OR<sup>1</sup>; and  $D^1$  is H. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is Cl; and  $D^1$  is H. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $R^1$ ; and  $D^1$  is H. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is NHR<sup>1</sup>; and  $D^1$  is H. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is NHR<sup>1</sup>; and  $D^1$  is Cl. In another embodiment of Formula

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(III),  $A^1$  is N;  $B^1$  is OR<sup>1</sup>; and  $D^1$  is H. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is Cl; and  $D^1$  is H. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is  $R^1$ ; and  $D^1$  is H.

In one embodiment of Formula (III),  $E^1$  is H. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is NHR<sup>1</sup>;  $E^1$  is H; and  $D^1$  is Cl. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is OR<sup>1</sup>;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is Cl;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is  $R^1$ ;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is Cl. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is OR<sup>1</sup>;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is Cl;  $D^1$  is H; and  $E^1$  is H. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is  $R^1$ ;  $D^1$  is H; and  $E^1$  is H.

In one embodiment of Formula (III),  $Y^1$  is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (III),  $Y^1$  is H. In another embodiment of Formula (III),  $Y^1$  is CN. In another embodiment of Formula (III),  $Y^1$  is F, Cl, Br, or I. In another embodiment of Formula (III),  $Y^1$  is CF<sub>3</sub>. In another embodiment of Formula (III),  $Y^1$  is SR<sup>17</sup>. In another embodiment of Formula (III),  $Y^1$  is OR<sup>17</sup>. In another embodiment of Formula (III),  $Y^1$  is NO<sub>2</sub>. In another embodiment of Formula (III),  $Y^1$  is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (III),  $Y^1$  is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (III),  $Y^1$  is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is NO<sub>2</sub>. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$  is H;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is NO<sub>2</sub>. In another embodiment of Formula (III),  $A^1$  is N;  $B^1$  is NHR<sup>1</sup>;  $D^1$  is H;  $E^1$  is H; and  $Y^1$  is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (III),  $Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (III),  $Y^1$  and  $B^1$ , together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$ ,  $G^1$ ,  $E^1$ , and  $D^1$  are independently selected H; and  $Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (III),  $A^1$  is  $C(A^2)$ ;  $A^2$ ,  $G^1$ ,  $E^1$ , and  $D^1$  are independently selected H; and  $Y^1$  and  $B^1$ , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>1</sup> is



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R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cycloalkyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>; R<sup>60</sup> is heterocycloalkyl; and R<sup>61</sup> is alkyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyran. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl. In another embodiment of Formula (III), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperiziny; and wherein the piperidinyl or piperiziny ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.

In one embodiment of Formula (III), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted. In one embodiment of Formula (III), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted with R<sup>7</sup>, OR<sup>7</sup>, OH, CN, or F. In

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another embodiment of Formula (III), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is substituted with R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, or N(R<sup>7</sup>)<sub>2</sub>.

In one embodiment of Formula (III), R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup> which are unsubstituted or substituted as defined herein.

In another embodiment of Formula (III), R<sup>7</sup> is R<sup>8</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>7</sup> is R<sup>9</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>7</sup> is R<sup>10</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>7</sup> is R<sup>11</sup> which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (III), R<sup>8</sup> is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (III), R<sup>9</sup> is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>9</sup> is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>9</sup> is furanyl; which is unsubstituted.

In one embodiment of Formula (III), R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is tetrahydrofuranyl, tetrahydropyran, morpholinyl, dioxan, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is tetrahydropyran; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>10</sup> is heterocycloalkyl which is fused with R<sup>10a</sup>, and R<sup>10a</sup> is heteroarene. In another embodiment of Formula (III), R<sup>10</sup> is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (III), R<sup>11</sup> is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>11</sup> is alkyl. In another embodiment of Formula (III), R<sup>11</sup> is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (III), R<sup>11</sup> is alkyl; which is substituted as defined herein. In another embodiment of Formula (III), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>, OR<sup>12</sup>, or CF<sub>3</sub>. In another embodiment of Formula (III), R<sup>11</sup> is alkyl; which is substituted with OR<sup>12</sup>; R<sup>12</sup> is R<sup>16</sup>; and R<sup>16</sup> is alkyl. In another embodiment of Formula (III), R<sup>11</sup> is alkyl; which is substituted with CF<sub>3</sub>. In another embodiment of Formula (III), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>; R<sup>12</sup> is R<sup>14</sup>; and R<sup>14</sup> is heteroaryl.

In one embodiment of Formula (III),

n, p, r, and q are each 0;

A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, F, Br, I, or Cl;

B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Br, I or Cl;

D<sup>1</sup> is H, F, Br, I, or Cl;

E<sup>1</sup> is H; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>,

SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>; or

Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and

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A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H;  
 R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>;  
 R<sup>4</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>5</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, CN, OH, F, Cl, Br or I;  
 R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, or R<sup>11</sup>;  
 R<sup>8</sup> is phenyl;  
 R<sup>9</sup> is heteroaryl;  
 R<sup>10</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R<sup>10A</sup>, R<sup>10A</sup> is heteroarene;  
 R<sup>11</sup> is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup> or CF<sub>3</sub>;  
 R<sup>12</sup> is R<sup>14</sup> or R<sup>16</sup>;  
 R<sup>14</sup> is heteroaryl;  
 R<sup>16</sup> is alkyl;  
 R<sup>17</sup> is R<sup>21</sup>;  
 R<sup>21</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, F, Cl, Br or I;  
 R<sup>22</sup> is R<sup>25</sup>;  
 R<sup>25</sup> is heterocycloalkyl;  
 wherein the cyclic moieties represented by Y<sup>1</sup> and B<sup>1</sup> together, R<sup>4</sup>, R<sup>8</sup>, R<sup>10</sup>, and R<sup>25</sup>, are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NHS(O)R<sup>57</sup>, OH, CN, (O), F, Cl, Br or I;  
 R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;  
 R<sup>57</sup> is R<sup>58</sup>, R<sup>60</sup> or R<sup>61</sup>;  
 R<sup>58</sup> is phenyl;  
 R<sup>60</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>61</sup> is alkyl which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, C(O)OH, CN, F, Cl, Br or I;  
 R<sup>62</sup> is R<sup>65</sup>, or R<sup>66</sup>;  
 R<sup>65</sup> is cycloalkyl, or heterocycloalkyl;  
 R<sup>66</sup> is alkyl which is unsubstituted or substituted with OR<sup>67</sup>;  
 R<sup>67</sup> is alkyl;  
 wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, and R<sup>60</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, F, Cl, Br or I;  
 R<sup>68</sup> is R<sup>71</sup> or R<sup>72</sup>;  
 R<sup>71</sup> is heterocycloalkyl; and  
 R<sup>72</sup> is alkyl, which is unsubstituted or substituted with one or two F.

Still another embodiment pertains to compounds having Formula (III), which are

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-yl-methoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-naphthyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-yl-methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-yl-methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{{3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-yl-methoxy)phenyl} sulfonyl}-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(4-morpholin-4-yl-cyclohexyl)amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-{{5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl} sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5-({4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl} amino} sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide;

N-{{5-bromo-6-(1-methylpiperidin-4-yl)methoxy}pyridin-3-yl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-{{5-cyano-6-(1,4-dioxan-2-yl-methoxy)pyridin-3-yl} sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{{5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl) amino]phenyl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(1-acetyl piperidin-4-yl)amino]-3-nitrophenyl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl) amino]phenyl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl) amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-{{5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl} sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{{2-(2-methoxyethoxy)ethyl} sulfonyl} phenyl) sulfonyl]-4-(4-{{2-(4-chlorophenyl)-4,

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4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-{{2-(2-methoxyethoxy) ethyl} sulfonyl}-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{{5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

15 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-{{4-({4-[(bis(cyclopropylmethyl)amino] cyclohexyl)amino]-3-nitrophenyl} sulfonyl)-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl) methyl]amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(morpholin-3-ylmethyl) amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

35 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-{{5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl} sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

40 4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-oxo-3,4-dihydroquinazolin-6-yl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 3-{{4-({4-({4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl} amino} sulfonyl)-2-nitrophenoxymethyl} morpholine-4-carboxylate;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-{{4-(morpholin-3-ylmethoxy)-3-nitrophenyl} sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({4-{{1-(1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

60 N-[(4-chloro-3-nitrophenyl) sulfonyl]-4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl} methyl} piperazin-1-yl)-N-({3-nitro-4-{{1-(2,2,2-trifluoroethyl) piperidin-4-yl} amino} phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-(2,2-difluoroethyl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-morpholin-4-ylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(dicyclopropylamino)cyclohexyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-bromo-6-[(4-ethylmorpholin-3-yl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methoxy]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-ylpiperidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxidothiomorpholin-4-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({4-[(4-aminotetrahydro-2H-pyran-4-yl)methyl]amino]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-mor-

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pholin-4-ylcyclohexyl)amino]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cis-3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-ylazetidin-3-yl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydrofuran-3-ylazetidin-3-yl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenyl)sulfonyl)benzamide;

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(cyclopropylamino)cyclohexyl]amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-({4-({4-({4-({2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyr-



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rolo[2,3-b]pyridin-5-yloxy)benzoyl]amino)sulfonyl]-2-nitrophenoxymethyl]-4-fluoropiperidine-1-carboxylate; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methoxy)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-methylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(2-methoxyethyl)morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; N-([4-([4-acetylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([4-(1-cyclobutylpiperidin-4-yl)amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3S)-1-cyclopropylpyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([1-tetrahydrofuran-3-yl]piperidin-4-yl)amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-cyclopropylpyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-([3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3-hydroxy-2,2-dimethylpropyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(methylsulfonyl)piperidin-3-yl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; N-([4-([1-acetyl]piperidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1-(methylsulfonyl)pyrrolidin-3-yl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; N-([4-([1-acetyl]pyrrolidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; N-([4-([3R)-1-acetyl]pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1R,3R)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1S,3S)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1S,3R)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([1R,3S)-3-hydroxycyclopentyl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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clopenty]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(2-fluoroethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(2,2-difluoroethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluoro-1-oxetan-3-ylpiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl]methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclobutyl)morpholin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydrofuran-3-yl)morpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3-(trifluoro-

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romethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-methoxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1,4-dioxaspiro[4.5]dec-8-ylamino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-N-[(4-{[(4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(trifluoromethyl)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-hydroxybenzyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(methylsulfonyl)amino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(1-oxetan-3-ylpiperidin-4-yl)methoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(3-(dimethylamino)propoxy]benzyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(2-morpholin-4-ylethoxy)benzyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(E)-4-hydroxy-1-adamantyl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(Z)-4-hydroxy-1-adamantyl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy]-3-nitrophenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[(1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({(3R)-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[6-[(4-fluorotetrahydro-2H-

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pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl}amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-([2-(2-methoxyethoxy)ethyl]morpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(cyanomethyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-({[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

2-([4-([4-([4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino)methyl)morpholin-4-yl]acetic acid;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl]amino)phenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-1[(4-cyclopropyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

ethyl 4-(4-{[4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([4-(morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide);

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-({[(3R)-1-(oxetan-



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3-yl)pyrrolidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(4-{[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-(2-methoxyethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-cyanomethyl)piperidin-3-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluoro-1-methylpiperidin-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl)amino]piperazine-1-carboxylate;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-(pentafluoro- $\lambda^6$ -sulfanyl)-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-[(4-{[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-fluoro-6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-{[1-(cyanomethyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-(2-methoxyethoxy)ethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)



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azetidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-((2R)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-((2S)-4-(N,N-dimethylglycyl)morpholin-2-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[[1-(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-((3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]ethoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[[1-(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-((trans-4-cyanocyclohexyl)methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-(3-furylmethoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[[1-(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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N-[(5-chloro-6-[[1-(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

5 N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

10 N-[(3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[3-cyano-4-(tetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

15 N-[(5-chloro-6-[[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

20 N-[(3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

25 N-[(3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

30 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

35 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(5-chloro-6-[2-(tetrahydrofuran-2-yl)ethoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

40 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-[[3-(cyclopropylamino)propyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-(2-methoxyethoxy)pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

45 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[5-fluoro-6-(tetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

50 N-[(3-chloro-4-[[1-(methoxyacetyl)piperidin-4-yl]methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

55 N-[(3-chloro-4-[[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

60 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-[[6-(tetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl]benzamide;

65 N-[(5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[trans-4-(morpholin-4-yl)cyclohexyl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-[cyclopropyl(1,3-thiazol-5-ylmethyl)amino]propyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-[cyclopropyl(oxetan-3-yl)amino]propyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(2S)-4-cyclopropylmorpholin-2-yl]methoxyl]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

methyl 2-[[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl]amino]methyl]morpholine-4-carboxylate;

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2-[[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]-2-nitrophenyl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-[cyclobutyl(cyclopropyl)amino]propyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-4-cyclopropylmorpholin-2-yl]methyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({5-chloro-6-[(4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methyl]amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-({3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-{[(4-cyclopropylmorpholin-2-yl)methyl]amino}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-[[[2-chloro-4-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl]amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

(2S)-2-[[[3-chloro-5-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl]oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

N-[(5-chloro-6-[(4-cyclopropylmorpholin-2-yl)methyl]amino]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

2-[[[3-chloro-5-[[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyr-

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rolo[2,3-b]pyridin-5-yloxy)benzoyl)sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(3,3-difluoropyrrolidin-1-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2,2-difluorocyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

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ylcyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

N-[(3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2-cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[2-oxaspiro[3.5]non-7-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyano-4-methylcyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(6-{[(trans-4-hydroxy-4-methylcyclohexyl)methyl]amino}-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-cyano-6-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;



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N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-{{4-({4-(methoxymethyl)cyclohexyl}methyl)amino}-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)benzamide;

4-(4-{{2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl}methyl}piperazin-1-yl)-N-[(5-chloro-6-[[1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-([[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino)-5-nitropyridin-3-yl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (IV)

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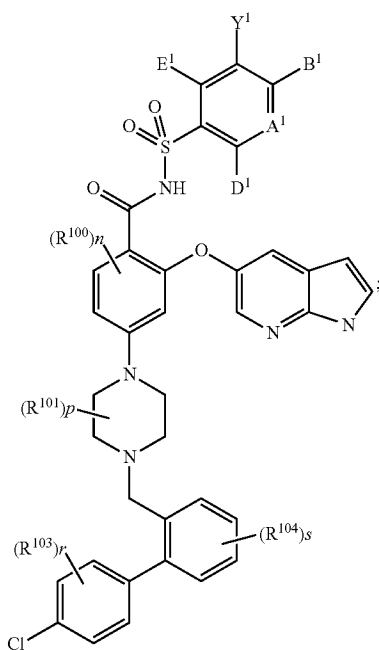
OR<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is R<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is N; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is N; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is N; and B<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is N; and B<sup>1</sup> is R<sup>1</sup>.

In one embodiment of Formula (IV), D<sup>1</sup> is H or Cl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H.

In one embodiment of Formula (IV), E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

In one embodiment of Formula (IV), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (IV), Y<sup>1</sup> is H. In another embodiment of Formula (IV), Y<sup>1</sup> is CN. In another embodiment of Formula (IV), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (IV), Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (IV), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (IV), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (IV), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (IV), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (IV), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (IV), Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (IV), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (IV), Y<sup>1</sup> and B<sup>1</sup>, together  
65 with the atoms to which they are attached, are benzene. In  
another embodiment of Formula (IV), Y<sup>1</sup> and B<sup>1</sup>, together  
with the atoms to which they are attached, are heteroarene. In



and therapeutically acceptable salts, and metabolites thereof, wherein A<sup>1</sup>, B<sup>1</sup>, D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are as described herein for Formula (I); R<sup>100</sup> is as described for substituents on R<sup>26</sup>; n is 0, 1, 2, or 3; R<sup>101</sup> is as described for substituents on R<sup>311</sup>; p is 0, 1, 2, 3, 4, 5, or 6; R<sup>104</sup> is as described for substituents on R<sup>38</sup>; s is 0, 1, 2, 3, 4, 5, or 6; R<sup>103</sup> is as described for substituents on R<sup>58</sup>; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (IV), n, p, r, and s are each 0.

In one embodiment of Formula (IV),  $A^1$  is N. In another embodiment of Formula (IV),  $A^1$  is C( $A^2$ ). In another embodiment of Formula (IV),  $A^1$  is C( $A^2$ ); and  $A^2$  is H, F, Cl, Br, or I. In another embodiment of Formula (IV),  $A^1$  is C( $A^2$ ); and  $A^2$  is H.

In one embodiment of Formula (IV), B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is



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another embodiment of Formula (IV),  $A^1$  is  $C(A^2)$ ;  $A^2$ ,  $G^1$ ,  $E^1$ , and  $D^1$  are independently selected H; and  $Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV),  $A^1$  is  $C(A^2)$ ;  $A^2$ ,  $G^1$ ,  $E^1$ , and  $D^1$  are independently selected H; and  $Y^1$  and  $B^1$ , together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (IV),  $R^1$  is  $R^4$  or  $R^5$ . In one embodiment of Formula (IV),  $R^1$  is  $R^4$ . In one embodiment of Formula (IV),  $R^1$  is  $R^5$ . In one embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl. In one embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl.

In one embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein  $R^4$  is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is substituted with  $R^{57}$  or  $N(R^{57})_2$ . In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $R^{57}$ ; and  $R^{57}$  is  $R^{60}$ . In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ;  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{60}$ ; and  $R^{60}$  is heterocycloalkyl. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ;  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{60}$ ;  $R^{60}$  is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is substituted with  $N(R^{57})_2$ . In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $N(R^{57})_2$ . In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $N(R^{57})_2$ ;  $R^{57}$  is  $R^{61}$ ; and  $R^{61}$  is alkyl which is unsubstituted or substituted with  $R^{62}$ . In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{61}$ ; and  $R^{61}$  is alkyl which is unsubstituted or substituted with  $R^{62}$ ;  $R^{62}$  is  $R^{65}$ ; and  $R^{65}$  is cycloalkyl. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{61}$ ; and  $R^{61}$  is alkyl which is substituted with  $R^{62}$ ;  $R^{62}$  is  $R^{65}$ ; and  $R^{65}$  is cyclopropyl.

In one embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl; wherein  $R^4$  is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with  $R^{57}$ . In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ; and  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with  $R^{57}$ ; and  $R^{57}$  is  $R^{60}$  or  $R^{61}$ . In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{60}$  or  $R^{61}$ ;  $R^{60}$  is heterocycloalkyl; and  $R^{61}$  is alkyl. In another embodiment of Formula

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(IV),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{60}$ ;  $R^{60}$  is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranyl. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{61}$ ;  $R^{61}$  is alkyl; and the alkyl  $R^{57}$  is methyl. In another embodiment of Formula (IV),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with  $C(O)OR^{57}$ ;  $R^{57}$  is  $R^{61}$ ;  $R^{61}$  is alkyl; and the alkyl is methyl.

In one embodiment of Formula (IV),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is unsubstituted or substituted. In one embodiment of Formula (IV),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is unsubstituted or substituted with  $R^7$ ,  $OR^7$ ,  $OH$ ,  $CN$ , or  $F$ . In another embodiment of Formula (IV),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is substituted with  $R^7$ ,  $OR^7$ ,  $NHR^7$ , or  $N(R^7)_2$ .

In one embodiment of Formula (IV),  $R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$  or  $R^{11}$  which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^7$  is  $R^8$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^7$  is  $R^9$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^7$  is  $R^{10}$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^7$  is  $R^{11}$  which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (IV),  $R^8$  is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (IV),  $R^9$  is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^9$  is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^9$  is furanyl; which is unsubstituted.

In one embodiment of Formula (IV),  $R^{10}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{10}$  is heterocycloalkyl which is fused with  $R^{10,4}$ ; and  $R^{10,4}$  is heteroarene. In another embodiment of Formula (IV),  $R^{10}$  is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (IV),  $R^{11}$  is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{11}$  is alkyl. In another embodiment of Formula (IV),  $R^{11}$  is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (IV),  $R^{11}$  is alkyl; which is substituted as defined herein. In another embodiment of Formula (IV),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ,  $OR^{12}$ , or  $CF_3$ .

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In another embodiment of Formula (IV), R<sup>11</sup> is alkyl; which is substituted with OR<sup>12</sup>; R<sup>12</sup> is R<sup>16</sup>; and R<sup>16</sup> is alkyl. In another embodiment of Formula (IV), R<sup>11</sup> is alkyl; which is substituted with CF<sub>3</sub>. In another embodiment of Formula (IV), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>, R<sup>12</sup> is R<sup>14</sup>, and R<sup>14</sup> is heteroaryl.

In one embodiment of Formula (IV),

n, p, r, and s are each 0;

A<sup>1</sup> is N or C(A<sup>2</sup>);

A<sup>2</sup> is H, F, Br, I, or Cl;

B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Br, I or Cl;

D<sup>1</sup> is H, F, Br, I, or Cl;

E<sup>1</sup> is H; and

Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>; or

Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and

A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H;

R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>;

R<sup>4</sup> is cycloalkyl, or heterocycloalkyl;

R<sup>5</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, CN, OH, F, Cl, Br or I;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, or R<sup>11</sup>;

R<sup>8</sup> is phenyl;

R<sup>9</sup> is heteroaryl;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R<sup>10A</sup>, R<sup>10A</sup> is heteroarene;

R<sup>11</sup> is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup> or CF<sub>3</sub>;

R<sup>12</sup> is R<sup>14</sup> or R<sup>16</sup>;

R<sup>14</sup> is heteroaryl;

R<sup>16</sup> is alkyl;

R<sup>17</sup> is R<sup>21</sup>;

R<sup>21</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>25</sup>;

R<sup>25</sup> is heterocycloalkyl;

wherein the cyclic moieties represented by Y<sup>1</sup> and B<sup>1</sup> together, R<sup>4</sup>, R<sup>8</sup>, R<sup>10</sup>, and R<sup>25</sup>, are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NHS(O)R<sup>57</sup>, OH, CN, (O), F, Cl, Br or I;

R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;

R<sup>57</sup> is R<sup>58</sup>, R<sup>60</sup> or R<sup>61</sup>;

R<sup>58</sup> is phenyl;

R<sup>60</sup> is cycloalkyl, or heterocycloalkyl;

R<sup>61</sup> is alkyl which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, C(O)OH, CN, F, Cl, Br or I;

R<sup>62</sup> is R<sup>65</sup>, or R<sup>66</sup>;

R<sup>65</sup> is cycloalkyl, or heterocycloalkyl;

R<sup>66</sup> is alkyl which is unsubstituted or substituted with OR<sup>67</sup>;

R<sup>67</sup> is alkyl;

wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, and R<sup>60</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, F, Cl, Br or I;

R<sup>68</sup> is R<sup>71</sup> or R<sup>72</sup>;

R<sup>71</sup> is heterocycloalkyl; and

R<sup>72</sup> is alkyl, which is unsubstituted or substituted with one or two F.

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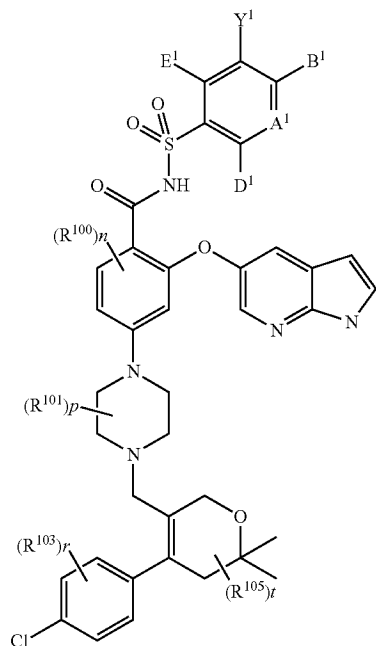
Still another embodiment pertains to compounds having Formula (V), which are

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide; and therapeutically acceptable salts, and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (V)

(V)



and therapeutically acceptable salts, and metabolites thereof, wherein A<sup>1</sup>, B<sup>1</sup>, D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are as described herein for Formula (I); R<sup>100</sup> is as described for substituents on R<sup>26</sup>; n is 0, 1, 2, or 3; R<sup>101</sup> is as described for substituents on R<sup>30</sup>; p is 0, 1, 2, 3, 4, 5, or 6; R<sup>105</sup> is as described for substituents on R<sup>40</sup>; t is 0, 1, 2, 3, or 4; R<sup>103</sup> is as described for substituents on R<sup>58</sup>; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (V), n, p, r, and t are each 0.

In one embodiment of Formula (V), A<sup>1</sup> is N. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>). In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); and A<sup>2</sup> is H, F, Cl, Br, or I. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); and A<sup>2</sup> is H.

In one embodiment of Formula (V), B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is R<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is N; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is N; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (V), A<sup>1</sup> is N; and B<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is N; and B<sup>1</sup> is R<sup>1</sup>.

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In one embodiment of Formula (V), D<sup>1</sup> is H or Cl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H.

In one embodiment of Formula (V), E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

In one embodiment of Formula (V), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (V), Y<sup>1</sup> is H. In another embodiment of Formula (V), Y<sup>1</sup> is CN. In another embodiment of Formula (V), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (V), Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (V), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (V), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (V), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (V), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (V), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (V), Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (V), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (V), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (V), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (V), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

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In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>; R<sup>60</sup> is heterocycloalkyl; and R<sup>61</sup> is alkyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl is tetrahydropyranlyl. In another embodiment of Formula (V), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup>

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is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with  $R^{57}$ ;  $R^{57}$  is  $R^{61}$ ;  $R^{61}$  is alkyl; and the alkyl is methyl. In another embodiment of Formula (V),  $R^1$  is  $R^4$ ;  $R^4$  is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with  $C(O)OR^{57}$ ;  $R^{57}$  is  $R^{61}$ ;  $R^{61}$  is alkyl; and the alkyl is methyl.

In one embodiment of Formula (V),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is unsubstituted or substituted. In one embodiment of Formula (V),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is unsubstituted or substituted with  $R^7$ ,  $OR^7$ ,  $OH$ ,  $CN$ , or  $F$ . In another embodiment of Formula (V),  $R^1$  is  $R^5$ ; and  $R^5$  is alkyl which is substituted with  $R^7$ ,  $OR^7$ ,  $NHR^7$ , or  $N(R^7)_2$ .

In one embodiment of Formula (V),  $R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$  or  $R^{11}$  which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^7$  is  $R^8$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^7$  is  $R^9$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^7$  is  $R^{10}$  which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^7$  is  $R^{11}$  which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (V),  $R^8$  is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (V),  $R^9$  is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^9$  is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^9$  is furanyl; which is unsubstituted.

In one embodiment of Formula (V),  $R^{10}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{10}$  is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{10}$  is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxanyl, oxetanyl, piperidinyl, or pyrrolidinyl, which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{10}$  is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{10}$  is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{10}$  is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{10}$  is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{10}$  is heterocycloalkyl which is fused with  $R^{10A}$ ; and  $R^{10A}$  is heteroarene. In another embodiment of Formula (V),  $R^{10}$  is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (V),  $R^{11}$  is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{11}$  is alkyl. In another embodiment of Formula (V),  $R^{11}$  is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (V),  $R^{11}$  is alkyl; which is substituted as defined herein. In another embodiment of Formula (V),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ,  $OR^{12}$ , or  $CF_3$ . In another embodiment of Formula (V),  $R^{11}$  is alkyl; which is substituted with  $OR^{12}$ ;  $R^{12}$  is  $R^{16}$ ; and  $R^{16}$  is alkyl. In another embodiment of Formula (V),  $R^{11}$  is alkyl; which is substituted with  $CF_3$ . In another embodiment of Formula (V),  $R^{11}$  is alkyl; which is substituted with  $R^{12}$ ;  $R^{12}$  is  $R^{14}$ ; and  $R^{14}$  is heteroaryl.

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In one embodiment of Formula (V),

$n$ ,  $p$ ,  $r$ , and  $t$  are each 0;

$A^1$  is  $N$  or  $C(A^2)$ ;

$A^2$  is  $H$ ,  $F$ ,  $Br$ ,  $I$ , or  $Cl$ ;

$B^1$  is  $R^1$ ,  $OR^1$ ,  $NHR^1$ ,  $NHC(O)R^1$ ,  $F$ ,  $Br$ ,  $I$  or  $Cl$ ;

$D^1$  is  $H$ ,  $F$ ,  $Br$ ,  $I$ , or  $Cl$ ;

$E^1$  is  $H$ ; and

$Y^1$  is  $H$ ,  $CN$ ,  $NO_2$ ,  $F$ ,  $Cl$ ,  $Br$ ,  $I$ ,  $CF_3$ ,  $R^{17}$ ,  $OR^{17}$ ,  $SR^{17}$ ,  $SO_2R^{17}$ , or  $C(O)NH_2$ ; or

$Y^1$  and  $B^1$ , together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and  $A^2$ ,  $D^1$ , and  $E^1$  are independently selected  $H$ ;

$R^1$  is  $R^4$  or  $R^5$ ;

$R^4$  is cycloalkyl, or heterocycloalkyl;

$R^5$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^7$ ,  $OR^7$ ,  $NHR^7$ ,  $N(R^7)_2$ ,  $CN$ ,  $OH$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^7$  is  $R^8$ ,  $R^9$ ,  $R^{10}$ , or  $R^{11}$ ;

$R^8$  is phenyl;

$R^9$  is heteroaryl;

$R^{10}$  is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with  $R^{10A}$ ;  $R^{10A}$  is heteroarene;

$R^{11}$  is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{12}$ ,  $OR^{12}$  or  $CF_3$ ;

$R^{12}$  is  $R^{14}$  or  $R^{16}$ ;

$R^{14}$  is heteroaryl;

$R^{16}$  is alkyl;

$R^{17}$  is  $R^{21}$ ;

$R^{21}$  is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{22}$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{22}$  is  $R^{25}$ ;

$R^{25}$  is heterocycloalkyl;

wherein the cyclic moieties represented by  $Y^1$  and  $B^1$  together,  $R^4$ ,  $R^8$ ,  $R^{10}$ , and  $R^{25}$ , are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected  $R^{57A}$ ,  $R^{57}$ ,  $OR^{57}$ ,  $SO_2R^{57}$ ,  $C(O)R^{57}$ ,  $CO(O)R^{57}$ ,  $C(O)N(R^{57})_2$ ,  $NH_2$ ,  $NHR^{57}$ ,  $N(R^{57})_2$ ,  $NHC(O)R^{57}$ ,  $NHS(O)_2R^{57}$ ,  $OH$ ,  $CN$ ,  $(O)$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{57A}$  is spiroalkyl, or spiroheteroalkyl;

$R^{57}$  is  $R^{58}$ ,  $R^{60}$  or  $R^{61}$ ;

$R^{58}$  is phenyl;

$R^{60}$  is cycloalkyl, or heterocycloalkyl;

$R^{61}$  is alkyl which is unsubstituted or substituted with one or two or three of independently selected  $R^{62}$ ,  $OR^{62}$ ,  $N(R^{62})_2$ ,  $C(O)OH$ ,  $CN$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{62}$  is  $R^{65}$ , or  $R^{66}$ ;

$R^{65}$  is cycloalkyl, or heterocycloalkyl;

$R^{66}$  is alkyl which is unsubstituted or substituted with  $OR^{67}$ ;

$R^{67}$  is alkyl;

wherein the cyclic moieties represented by  $R^{57A}$ ,  $R^{58}$ , and  $R^{60}$  are unsubstituted or substituted with one or two or three or four of independently selected  $R^{68}$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

$R^{68}$  is  $R^{71}$  or  $R^{72}$ ;

$R^{71}$  is heterocycloalkyl; and

$R^{72}$  is alkyl, which is unsubstituted or substituted with one or two  $F$ .



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Still another embodiment pertains to a compound having Formula (V), which is

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl}sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

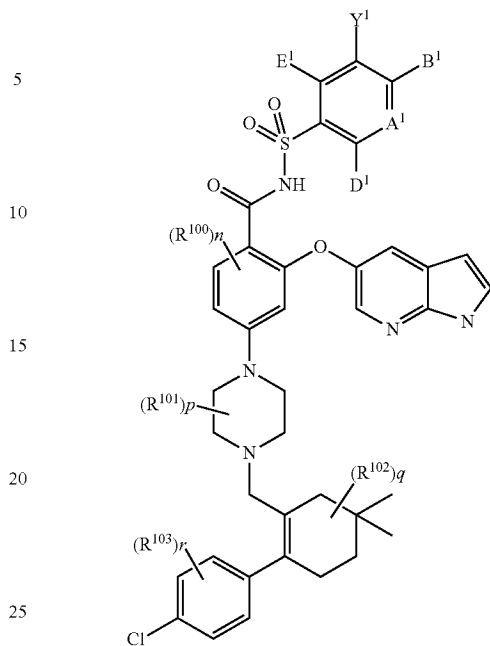
4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts, and metabolites thereof.

In another aspect, the present invention provides compounds of Formula (VI)

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(VI)



and therapeutically acceptable salts, and metabolites thereof, wherein A<sup>1</sup>, B<sup>1</sup>, D<sup>1</sup>, E<sup>1</sup>, and Y<sup>1</sup> are as described herein for Formula (I); R<sup>100</sup> is as described for substituents on R<sup>26</sup>; n is 0, 1, 2, or 3; R<sup>101</sup> is as described for substituents on R<sup>30</sup>; p is 0, 1, 2, 3, 4, 5, or 6; R<sup>102</sup> is as described for substituents on R<sup>40</sup>; q is 0, 1, 2, 3, 4, 5, or 6; R<sup>103</sup> is as described for substituents on R<sup>58</sup>; and r is 0, 1, 2, 3, or 4.

In one embodiment of Formula (VI), n, p, r, and q are each 0.

In one embodiment of Formula (VI), A<sup>1</sup> is N. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>). In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); and A<sup>2</sup> is H, F, Cl, Br, or I. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); and A<sup>2</sup> is H.

In one embodiment of Formula (VI), B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Cl, Br, or I. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is Cl. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; and B<sup>1</sup> is R<sup>1</sup>. In another embodiment of Formula (VI), A<sup>1</sup> is N; and B<sup>1</sup> is NHR<sup>1</sup>. In another embodiment of Formula (VI), A<sup>1</sup> is N; and B<sup>1</sup> is OR<sup>1</sup>. In another embodiment of Formula (VI), A<sup>1</sup> is N; and B<sup>1</sup> is Cl. In another embodiment of Formula (VI), A<sup>1</sup> is N; and B<sup>1</sup> is R<sup>1</sup>.

In one embodiment of Formula (VI), D<sup>1</sup> is H or Cl. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is Cl. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; and D<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is Cl; and D<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; and D<sup>1</sup> is H.

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In one embodiment of Formula (VI), E<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; E<sup>1</sup> is H; and D<sup>1</sup> is Cl. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is OR<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is Cl; D<sup>1</sup> is H; and E<sup>1</sup> is H. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is R<sup>1</sup>; D<sup>1</sup> is H; and E<sup>1</sup> is H.

In one embodiment of Formula (VI), Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>. In another embodiment of Formula (VI), Y<sup>1</sup> is H. In another embodiment of Formula (VI), Y<sup>1</sup> is CN. In another embodiment of Formula (VI), Y<sup>1</sup> is F, Cl, Br, or I. In another embodiment of Formula (VI), Y<sup>1</sup> is CF<sub>3</sub>. In another embodiment of Formula (VI), Y<sup>1</sup> is SR<sup>17</sup>. In another embodiment of Formula (VI), Y<sup>1</sup> is OR<sup>17</sup>. In another embodiment of Formula (VI), Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (VI), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is as defined herein. In another embodiment of Formula (VI), Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl. In another embodiment of Formula (VI), Y<sup>1</sup> is R<sup>17</sup>; wherein R<sup>17</sup> is alkynyl. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (VI), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup> is H; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub> or SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl or alkynyl. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is NO<sub>2</sub>. In another embodiment of Formula (VI), A<sup>1</sup> is N; B<sup>1</sup> is NHR<sup>1</sup>; D<sup>1</sup> is H; E<sup>1</sup> is H; and Y<sup>1</sup> is SO<sub>2</sub>R<sup>17</sup>; wherein R<sup>17</sup> is alkyl substituted with three F.

In one embodiment of Formula (IV), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV), Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene. In another embodiment of Formula (IV), A<sup>1</sup> is C(A<sup>2</sup>); A<sup>2</sup>, G<sup>1</sup>, E<sup>1</sup>, and D<sup>1</sup> are independently selected H; and Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are heteroarene.

In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>. In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>. In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>5</sup>. In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl. In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl or heterocycloalkyl. In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl. In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl.

In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted as defined herein. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl

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ring is substituted with R<sup>57</sup> or N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; and R<sup>60</sup> is heterocycloalkyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup>; R<sup>60</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is morpholinyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cyclohexyl ring is substituted with N(R<sup>57</sup>)<sub>2</sub>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is unsubstituted or substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cycloalkyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is cycloalkyl; wherein the cycloalkyl ring is cyclohexyl; and wherein the cyclohexyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; and R<sup>61</sup> is alkyl which is substituted with R<sup>62</sup>; R<sup>62</sup> is R<sup>65</sup>; and R<sup>65</sup> is cyclopropyl.

In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein R<sup>4</sup> is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted as defined herein. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; and R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the heterocycloalkyl ring is substituted with R<sup>57</sup>; and R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>60</sup> or R<sup>61</sup>; R<sup>60</sup> is heterocycloalkyl; and R<sup>61</sup> is alkyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with R<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>4</sup>; R<sup>4</sup> is heterocycloalkyl; wherein the heterocycloalkyl ring is piperidinyl or piperizinyl; and wherein the piperidinyl or piperizinyl ring is substituted with C(O)OR<sup>57</sup>; R<sup>57</sup> is R<sup>61</sup>; R<sup>61</sup> is alkyl; and the alkyl is methyl.

In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted. In one embodiment of Formula (VI), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is unsubstituted or substituted with R<sup>7</sup>, OR<sup>7</sup>, OH, CN, or F. In another embodiment of Formula (VI), R<sup>1</sup> is R<sup>5</sup>; and R<sup>5</sup> is alkyl which is substituted with R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, or N(R<sup>7</sup>)<sub>2</sub>.

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In one embodiment of Formula (VI), R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> or R<sup>11</sup> which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>7</sup> is R<sup>8</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>7</sup> is R<sup>9</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>7</sup> is R<sup>10</sup> which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>7</sup> is R<sup>11</sup> which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (VI), R<sup>8</sup> is phenyl which is unsubstituted or substituted as defined herein.

In one embodiment of Formula (VI), R<sup>9</sup> is heteroaryl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>9</sup> is furanyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>9</sup> is furanyl; which is unsubstituted.

In one embodiment of Formula (VI), R<sup>10</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, heterocycloalkyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is heterocycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, dioxan-yl, oxetanyl, piperidinyl, or pyrrolidinyl; which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is tetrahydropyranyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is morpholinyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is cycloalkyl which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is cyclohexyl, cyclopropyl, cyclobutyl, or bicyclo[2.2.1]heptanyl, which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>10</sup> is heterocycloalkyl which is fused with R<sup>10A</sup>; and R<sup>10A</sup> is heteroarene. In another embodiment of Formula (VI), R<sup>10</sup> is 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl.

In one embodiment of Formula (VI), R<sup>11</sup> is alkyl, alkenyl or alkynyl which are unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl. In another embodiment of Formula (VI), R<sup>11</sup> is methyl; which is unsubstituted or substituted as defined herein. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl; which is substituted as defined herein. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl; which is substituted with R<sup>12</sup>, OR<sup>12</sup>, or CF<sub>3</sub>. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl, which is substituted with OR<sup>12</sup>; R<sup>12</sup> is R<sup>16</sup>; and R<sup>16</sup> is alkyl. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl; which is substituted with CF<sub>3</sub>. In another embodiment of Formula (VI), R<sup>11</sup> is alkyl, which is substituted with R<sup>12</sup>; R<sup>12</sup> is R<sup>14</sup>; and R<sup>14</sup> is heteroaryl.

In one embodiment of Formula (VI),  
n, p, r, and q are each 0;  
A<sup>1</sup> is N or C(A<sup>2</sup>);  
A<sup>2</sup> is H, F, Br, I, or Cl;  
B<sup>1</sup> is R<sup>1</sup>, OR<sup>1</sup>, NHR<sup>1</sup>, NHC(O)R<sup>1</sup>, F, Br, I or Cl;  
D<sup>1</sup> is H, F, Br, I, or Cl;  
E<sup>1</sup> is H; and  
Y<sup>1</sup> is H, CN, NO<sub>2</sub>, F, Cl, Br, I, CF<sub>3</sub>, R<sup>17</sup>, OR<sup>17</sup>, SR<sup>17</sup>, SO<sub>2</sub>R<sup>17</sup>, or C(O)NH<sub>2</sub>; or  
Y<sup>1</sup> and B<sup>1</sup>, together with the atoms to which they are attached, are benzene, heteroarene, or heterocycloalkene; and  
A<sup>2</sup>, D<sup>1</sup>, and E<sup>1</sup> are independently selected H;  
R<sup>1</sup> is R<sup>4</sup> or R<sup>5</sup>;  
R<sup>4</sup> is cycloalkyl, or heterocycloalkyl;

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R<sup>5</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>7</sup>, OR<sup>7</sup>, NHR<sup>7</sup>, N(R<sup>7</sup>)<sub>2</sub>, CN, OH, F, Cl, Br or I;

R<sup>7</sup> is R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, or R<sup>11</sup>;

R<sup>8</sup> is phenyl;

R<sup>9</sup> is heteroaryl;

R<sup>10</sup> is cycloalkyl, cycloalkenyl, or heterocycloalkyl; each of which is unfused or fused with R<sup>10A</sup>, R<sup>10A</sup> is heteroarene;

R<sup>11</sup> is alkyl each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>12</sup>, OR<sup>12</sup> or CF<sub>3</sub>;

R<sup>12</sup> is R<sup>14</sup> or R<sup>16</sup>;

R<sup>14</sup> is heteroaryl;

R<sup>16</sup> is alkyl;

R<sup>17</sup> is R<sup>21</sup>;

R<sup>21</sup> is alkyl, or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>22</sup>, F, Cl, Br or I;

R<sup>22</sup> is R<sup>25</sup>;

R<sup>25</sup> is heterocycloalkyl;

wherein the cyclic moieties represented by Y<sup>1</sup> and B<sup>1</sup> together, R<sup>4</sup>, R<sup>8</sup>, R<sup>16</sup>, and R<sup>25</sup>, are independently unsubstituted, further unsubstituted, substituted or further substituted with one or two or three or four or five of independently selected R<sup>57A</sup>, R<sup>57</sup>, OR<sup>57</sup>, SO<sub>2</sub>R<sup>57</sup>, C(O)R<sup>57</sup>, CO(O)R<sup>57</sup>, C(O)N(R<sup>57</sup>)<sub>2</sub>, NH<sub>2</sub>, NHR<sup>57</sup>, N(R<sup>57</sup>)<sub>2</sub>, NHC(O)R<sup>57</sup>, NHS(O)R<sup>57</sup>, OH, CN, (O), F, Cl, Br or I;

R<sup>57A</sup> is spiroalkyl, or spiroheteroalkyl;

R<sup>57</sup> is R<sup>58</sup>, R<sup>11</sup> or R<sup>61</sup>;

R<sup>58</sup> is phenyl;

R<sup>60</sup> is cycloalkyl, or heterocycloalkyl;

R<sup>61</sup> is alkyl which is unsubstituted or substituted with one or two or three of independently selected R<sup>62</sup>, OR<sup>62</sup>, N(R<sup>62</sup>)<sub>2</sub>, C(O)OH, CN, F, Cl, Br or I;

R<sup>62</sup> is R<sup>65</sup>, or R<sup>66</sup>;

R<sup>65</sup> is cycloalkyl, or heterocycloalkyl;

R<sup>66</sup> is alkyl which is unsubstituted or substituted with OR<sup>67</sup>;

R<sup>67</sup> is alkyl;

wherein the cyclic moieties represented by R<sup>57A</sup>, R<sup>58</sup>, and R<sup>60</sup> are unsubstituted or substituted with one or two or three or four of independently selected R<sup>68</sup>, F, Cl, Br or I;

R<sup>68</sup> is R<sup>71</sup> or R<sup>72</sup>;

R<sup>71</sup> is heterocycloalkyl; and

R<sup>72</sup> is alkyl, which is unsubstituted or substituted with one or two F.

Still another embodiment pertains to a compound having Formula (VI), which is

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;  
4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts, and metabolites thereof. Pharmaceutical Compositions, Combination Therapies, Methods of Treatment, and Administration

Another embodiment comprises pharmaceutical compositions comprising a compound having Formula (I) and an excipient.



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Still another embodiment comprises methods of treating cancer in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having Formula (I).

Still another embodiment comprises methods of treating autoimmune disease in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating diseases during which anti-apoptotic Bcl-2 proteins are expressed, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I).

Still another embodiment pertains to methods of treating disease in a patient during which anti-apoptotic Bcl-2 proteins are expressed, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I). Still another embodiment pertains to compositions for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I).

Still another embodiment pertains to methods of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I).

Still another embodiment pertains to compositions for treating diseases during which are expressed anti-apoptotic Bcl-2 proteins, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to methods of treating disease in a patient during which are expressed anti-apoptotic Bcl-2 proteins, said methods comprising administering to the patient a therapeutically effective amount of a compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Still another embodiment pertains to compositions for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

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Still another embodiment pertains to methods of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a patient, said methods comprising administering to the patient a therapeutically effective amount of the compound having Formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Metabolites of compounds having Formula (I), produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases associated with anti-apoptotic Bcl-2 proteins.

Certain precursor compounds which may be metabolized in vitro or in vivo to form compounds having Formula (I) may also have utility for treating diseases associated with expression of anti-apoptotic Bcl-2 proteins.

Compounds having Formula (I) may exist as acid addition salts, basic addition salts or zwitterions. Salts of the compounds are prepared during isolation or following purification of the compounds. Acid addition salts of the compounds are those derived from the reaction of the compounds with an acid. For example, the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trifluoroacetic, para-toluenesulfonate, and undecanoate salts of the compounds are contemplated as being embraced by this invention. Basic addition salts of the compounds are those derived from the reaction of the compounds with the hydroxide, carbonate or bicarbonate of cations such as lithium, sodium, potassium, calcium, and magnesium.

The compounds having Formula (I) may be administered, for example, buccally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperitoneally intrasternally, intravenously, subcutaneously), rectally, topically, transdermally or vaginally.

Therapeutically effective amounts of compounds having Formula (I) depend on the recipient of the treatment, the disorder being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered. The amount of a compound of this invention having Formula (I) used to make a composition to be administered daily to a patient in a single dose or in divided doses is from about 0.03 to about 200 mg/kg body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

Compounds having Formula (I) may be administered with or without an excipient. Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants,



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perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

Excipients for preparation of compositions comprising a compound having Formula (I) to be administered orally in solid dosage form include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered ophthalmically or orally in liquid dosage forms include, for example, 1,3-butylene glycol, castor oil, corn oil, cottonseed oil, ethanol, fatty acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered osmotically include, for example, chlorofluorohydrocarbons, ethanol, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered parenterally include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having Formula (I) to be administered rectally or vaginally include, for example, cocoa butter, polyethylene glycol, wax and mixtures thereof.

Compounds having Formula (I) are expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, other apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNA's, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, etinoids/deltoids plant alkaloids,

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small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, and the like, and in combination with one or more of these agents.

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (V. R. Sutton, D. L. Vaux and J. A. Trapani, *J. of Immunology* 1997, 158 (12), 5783).

siRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH<sub>3</sub>-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/or the 3'-ends of a given strand. For example, siRNAs targeting Mcl-1 have been shown to enhance the activity of ABT-263, (i.e., N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide) or ABT-737 (i.e., N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) in multiple tumor cell lines (Tse et al, *Cancer Research* 2008, 68(9), 3421 and references therein).

Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, CLORE-TAZINE® (laromustine, VNP 40101M), cyclophosphamide,

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decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, TRE-ANDA® (bendamustine), treosulfan, rofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

Antimetabolites include ALIMTA® (pemetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA® (capecitabine), carmofur, LEUSTAT® (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferroxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-(3-D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethynylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR® (gemcitabine), hydroxyuracil, ALKERAN® (melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

Antivirals include ritonavir, hydroxychloroquine and the like.

Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, Aurora A-specific kinase inhibitors, Aurora B-specific kinase inhibitors and pan-Aurora kinase inhibitors and the like.

Bcl-2 protein inhibitors include AT-101 ((-)-gossypol), GENASENSE® (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4-(4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide (ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263), GX-070 (obatocicax) and the like.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (imatinib) and the like.

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

COX-2 inhibitors include ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX® (celecoxib), COX-189 (lumiracoxib), CT-3, DERA-MAXX® (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole, MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) and the like.

EGFR inhibitors include ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX® (cetuximab), HR3, IgA antibodies, IRESSA® (gefitinib), TARCEVA® (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB® (lapatinib) and the like.

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), HERCEPTIN® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (2C4, pertuzumab), TAK-165,

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GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecific antibodies, mAB AR-209, mAB 2B-1 and the like.

Histone deacetylase inhibitors include depsi-peptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB® (human recombinant antibody to HSP-90), NCS-683664, PU24FC1, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

Inhibitors of inhibitors of apoptosis proteins include HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

Antibody drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, SGN-75 and the like.

Activators of death receptor pathway include TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR4 and DR5) such as Apomab, conatumumab, ETR2-ST01, GDC0145, (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

Kinesin inhibitors include Eg5 inhibitors such as AZD4877, ARRY-520; CENPE inhibitors such as GSK923295A and the like.

JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCB018424 and the like.

MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, Torin 1 and the like.

Non-steroidal anti-inflammatory drugs include AMIGESIC® (salsalate), DOLOBID® (diflunisal), MOTRIN® (ibuprofen), ORUDIS® (ketoprofen), RELAFEN® (nabumetone), FELDENE® (piroxicam), ibuprofen cream, ALEVE® (naproxen) and NAPROSYN® (naproxen), VOLTAREN® (diclofenac), INDOCIN® (indomethacin), CLINORIL® (sulindac), TOLECTIN® (tolmetin), LODINE® (etodolac), TARDOL® (ketorolac), DAYPRO® (oxaprozin) and the like.

PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

Platinum chemotherapeutics include cisplatin, ELOXATIN® (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN® (carboplatin), satraplatin, picoplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

Phosphoinositide-3 kinase (PI3K) inhibitors include wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

VEGFR inhibitors include AVASTIN® (bevacizumab), ABT-869, AEE-788, ANGIOZYME™ (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, Colo.) and Chiron, (Emeryville, Calif.)), axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pegaptamib), NEXAVAR® (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), VEGF trap, ZACTIMA™ (vandetanib, ZD-6474) and the like.

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Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLE-NOXANE® (bleomycin), daunorubicin, CAELYX® or MYOCET® (liposomal doxorubicin), elsamitucin, epirubicin, glarubicin, ZAVEDOS® (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR® (valrubicin), zinostatin and the like.

Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR® (irinotecan hydrochloride), camptothecin, CARDIOXANE® (dexrazoxine), diflomotecan, edotecarin, ELLENCE or PHARMORUBICIN® (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarubicin, pixanthrone, rubitecan, sobuzoxane, SN-38, taf-luposide, topotecan and the like.

Antibodies include AVASTIN® (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzumab, CD20 antibodies types I and II and the like.

Hormonal therapies include ARIMIDEX® (anastrozole), AROMASIN (exemestane), arzoxifene, CASODEX® (bicalutamide), CETROTIDE® (cetrorelix), degarelix, deslorelin, DESOPAN® (trilostane), dexamethasone, DROGENIL® (flutamide), EVISTA® (raloxifene), AFEMA™ (fadrozole), FARESTON® (toremifene), FASLODEX® (fulvestrant), FEMARA® (letrozole), formestane, glucocorticoids, HECTOROL® (doxercalciferol), RENAGEL® (sevelamer carbonate), lasofoxifene, leuprolide acetate, MEGACE® (megesterol), MIFEPREX® (mifepristone), NILANDRON™ (nilutamide), NOLVADEX® (tamoxifen citrate), PLENAXIS™ (abarelix), prednisone, PROPECIA® (finasteride), rilostane, SUPREFACT® (buserelin), TRELSTAR® (luteinizing hormone releasing hormone (LHRH)), VANTAS® (Histrelin implant), VETORYL® (trilostane or modrostan), ZOLADEX® (fosreltin, goserelin) and the like.

Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitol (KH1060), fenretinide, PANRETIN® (aliretinoin), ATRAGEN® (liposomal tretinoin), TARGRETIN® (bexarotene), LGD-1550 and the like.

PARP inhibitors include ABT-888 (veliparib), olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

Proteasome inhibitors include VELCADE® (bortezomib), MG132, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE® (interferon gamma-1b) or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE®, (IFN- $\alpha$ ), BAM-002 (oxidized glutathione), BEROMUN® (tasonermin), BEXXAR® (tositumomab), CAMPATH® (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE® (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab, molgramostim, MYLOTARG™ (gemtuzumab ozogamicin), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pemtumomab (Y-muHMFg1), PROVENGE® (sipuleucel-T), sargarmostim, sizofilan, teceleukin,

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THERACYS® (Bacillus Calmette-Guerin), ubenimex, VIRULIZIN® (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodecaoxide (TCDO)), PROLEUKIN® (aldesleukin), ZADAXIN® (thymalfasin), ZENAPAX® (dacizumab), ZEVALIN® (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofuran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA® (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR® (gemcitabine), TOMUDEX® (ratitrexed), TROXATYL™ (triacytyluridine troxycitabine) and the like.

Purine analogs include LANVIS® (thioguanine) and PURI-NETHOL® (mercaptapurine).

Antimitotic agents include batimastat, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilone, XRP-9881 (larotaxel), vinflunine, ZK-EPO (synthetic epothilone) and the like.

Ubiquitin ligase inhibitors include MDM2 inhibitors, such as nultins, NEDD8 inhibitors such as MLN4924 and the like.

Compounds of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy and the like.

Additionally, compounds having Formula (I) may be combined with other chemotherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN® (Ad5CMV-p53 vaccine), ALTOCOR® or MEVACOR® (lovastatin), AMPLIGEN® (poly I:poly C12U, a synthetic RNA), APTOSYN® (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), AVAGE® (tazarotene), AVE-8062 (combreastatin derivative) BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CEAVAC® (cancer vaccine), CELEUK® (celmoleukin), CEPLINE® (histamine dihydrochloride), CERVARIX® (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CYPAT™ (cyproterone acetate), combrestatin A4P, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor) or TransMID-107R™ (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthone-4-acetic acid (DMXAA), eniluracil, EVI-ZON™ (squalamine lactate), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EP0906 (epithilone B), GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), GASTRIMMUNE®, GENA-SENSE®, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon- $\alpha$ , interferon- $\gamma$ , JUNOVAN™ or



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MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT® (AE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), ONCOVAX® (IL-2 Vaccine), ORATHECIN™ (rubitecan), OSIDEM® (antibody-based cell drug), OVAREX® MAb (murine monoclonal antibody), paclitaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REVLIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (*Streptomyces* staurospores), talabostat (PT100), TARGRETIN® (bexarotene), TAXOPREXIN® (DHA-paclitaxel), TELCYTA® (canfosfamide, TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFERADE™ (adenovector: DNA carrier containing the gene for tumor necrosis factor- $\alpha$ ), TRACLEER® or ZAVESCA® (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX® (arsenic trioxide), VIRULIZIN®, ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti-alphavbeta3 antibody), XCYTRIN® (motexafin gadolinium), XINLAY™ (atrasentan), XYOTAX™ (paclitaxel poliglumex), YONDELIS® (trabectedin), ZD-6126, ZINECARD® (dexrazoxane), ZOMETA® (zoledronic acid), zorubicin and the like.

Data

Determination of the utility of compounds having Formula (I) as binders to and inhibitors of anti-apoptotic Bcl-2 proteins was performed using the Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) Assay. Tb-anti-GST antibody was purchased from Invitrogen (Catalog No. PV4216).

#### Probe Synthesis

All reagents were used as obtained from the vendor unless otherwise specified. Peptide synthesis reagents including diisopropylethylamine (DIEA), dichloromethane (DCM), N-methylpyrrolidone (NMP), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), N-hydroxybenzotriazole (HOBt) and piperidine were obtained from Applied Biosystems, Inc. (ABI), Foster City, Calif. or American Bioanalytical, Natick, Mass. Preloaded 9-Fluorenylmethyloxycarbonyl (Fmoc) amino acid cartridges (Fmoc-Ala-OH, Fmoc-Cys(Trt)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Glu(tBu)-OH, Fmoc-Phe-OH, Fmoc-Gly-OH, Fmoc-His(Trt)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Met-OH, Fmoc-Asn(Trt)-OH, Fmoc-Pro-OH, Fmoc-Gln(Trt)-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Val-OH, Fmoc-Trp(Boc)-OH, Fmoc-Tyr(tBu)-OH) were obtained from ABI or Anaspec, San Jose, Calif. The peptide synthesis resin (Fmoc-Rink amide MBHA resin) and Fmoc-Lys(Mtt)-OH were obtained from Novabiochem, San Diego, Calif. Single-isomer 6-carboxyfluorescein succinimidyl ester

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(6-FAM-NHS) was obtained from Anaspec. Trifluoroacetic acid (TFA) was obtained from Oakwood Products, West Columbia, S.C. Thioanisole, phenol, triisopropylsilane (TIS), 3,6-dioxa-1,8-octanedithiol (DODT) and isopropanol were obtained from Aldrich Chemical Co., Milwaukee, Wis. Matrix-assisted laser desorption ionization mass-spectra (MALDI-MS) were recorded on an Applied Biosystems Voyager DE-PRO MS. Electrospray mass-spectra (ESI-MS) were recorded on Finnigan SSQ7000 (Finnigan Corp., San Jose, Calif.) in both positive and negative ion mode.

#### General Procedure for Solid-Phase Peptide Synthesis (SPPS)

Peptides were synthesized with, at most, 250  $\mu$ mol preloaded Wang resin/vessel on an ABI 433A peptide synthesizer using 250  $\mu$ mol scale FASTMOCT™ coupling cycles. Preloaded cartridges containing 1 mmol standard Fmoc-amino acids, except for the position of attachment of the fluorophore, where 1 mmol Fmoc-Lys(Mtt)-OH was placed in the cartridge, were used with conductivity feedback monitoring. N-terminal acetylation was accomplished by using 1 mmol acetic acid in a cartridge under standard coupling conditions.

#### Removal of 4-Methyltrityl (Mtt) from Lysine

The resin from the synthesizer was washed thrice with DCM and kept wet. 150 mL of 95:4:1 dichloromethane:triisopropylsilane:trifluoroacetic acid was flowed through the resin bed over 30 minutes. The mixture turned deep yellow then faded to pale yellow. 100 mL of DMF was flowed through the bed over 15 minutes. The resin was then washed thrice with DMF and filtered. Ninhydrin tests showed a strong signal for primary amine.

#### Resin Labeling with 6-Carboxyfluorescein-NHS (6-FAM-NHS)

The resin was treated with 2 equivalents 6-FAM-NHS in 1% DIEA/DMF and stirred or shaken at ambient temperature overnight. When complete, the resin was drained, washed thrice with DMF, thrice with (1 $\times$ DCM and 1 $\times$ methanol) and dried to provide an orange resin that was negative by ninhydrin test.

#### General Procedure for Cleavage and Deprotection of Resin-Bound Peptide

Peptides were cleaved from the resin by shaking for 3 hours at ambient temperature in a cleavage cocktail consisting of 80% TFA, 5% water, 5% thioanisole, 5% phenol, 2.5% TIS, and 2.5% EDT (1 mL/0.1 g resin). The resin was removed by filtration and rinsing twice with TFA. The TFA was evaporated from the filtrates, and product was precipitated with ether (10 mL/0.1 g resin), recovered by centrifugation, washed twice with ether (10 mL/0.1 g resin) and dried to give the crude peptide.

#### General Procedure for Purification of Peptides

The crude peptides were purified on a Gilson preparative HPLC system running Unipoint® analysis software (Gilson,



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Inc., Middleton, Wis.) on a radial compression column containing two 25×100 mm segments packed with Delta-Pak™ C18 15 μm particles with 100 Å pore size and eluted with one of the gradient methods listed below. One to two milliliters of crude peptide solution (10 mg/mL in 90% DMSO/water) was purified per injection. The peaks containing the product(s) from each run were pooled and lyophilized. All preparative runs were run at 20 mL/min with eluents as buffer A: 0.1% TFA-water and buffer B: acetonitrile.

#### General Procedure for Analytical HPLC

Analytical HPLC was performed on a Hewlett-Packard 1200 series system with a diode-array detector and a Hewlett-Packard 1046A fluorescence detector running HPLC 3D CHEMSTATION software version A.03.04 (Hewlett-Packard, Palo Alto, Calif.) on a 4.6×250 mm YMC column packed with ODS-AQ 5 μm particles with a 120 Å pore size and eluted with one of the gradient methods listed below after preequilibrating at the starting conditions for 7 minutes. Eluents were buffer A: 0.1% TFA-water and buffer B: acetonitrile. The flow rate for all gradients was 1 mL/min.

(SEQ ID NO: 1)

F-Bak: Peptide Probe Acetyl-GQVGRQLAIIGDK(6-FAM) -

INR-NH<sub>2</sub>

Fmoc-Rink amide MBHA resin was extended using the general peptide synthesis procedure to provide the protected resin-bound peptide (1.020 g). The Mtt group was removed, labeled with 6-FAM-NHS and cleaved and deprotected as described hereinabove to provide the crude product as an orange solid (0.37 g). This product was purified by RP-HPLC. Fractions across the main peak were tested by analytical RP-HPLC, and the pure fractions were isolated and lyophilized, with the major peak providing the title compound (0.0802 g) as a yellow solid; MALDI-MS  $m/z$ =2137.1 [(M+H)<sup>+</sup>].

(SEQ ID NO: 1)

Alternative Synthesis of Peptide Probe

F-Bak: Acetyl-GQVGRQLAIIGDK(6-FAM) -INR-NH<sub>2</sub>

The protected peptide was assembled on 0.25 mmol Fmoc-Rink amide MBHA resin (Novabiochem) on an Applied Biosystems 433A automated peptide synthesizer running FAST-

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MOC™ coupling cycles using pre-loaded 1 mmol amino acid cartridges, except for the fluorescein(6-FAM)-labeled lysine, where 1 mmol Fmoc-Lys(4-methyltrityl) was weighed into the cartridge. The N-terminal acetyl group was incorporated by putting 1 mmol acetic acid in a cartridge and coupling as described hereinabove. Selective removal of the 4-methyltrityl group was accomplished with a solution of 95:4:1 DCM: TIS:TFA (v/v/v) flowed through the resin over 15 minutes, followed by quenching with a flow of dimethylformamide. Single-isomer 6 carboxyfluorescein-NHS was reacted with the lysine side-chain in 1% DIEA in DMF and confirmed complete by ninhydrin testing. The peptide was cleaved from the resin and side-chains deprotected by treating with 80:5: 5:5:2.5:2.5 TFA/water/phenol/thioanisole/triisopropylsilane: 3,6-dioxo-1,8-octanedithiol (v/v/v/v/v/v), and the crude peptide was recovered by precipitation with diethyl ether. The crude peptide was purified by reverse-phase high-performance liquid chromatography, and its purity and identity were confirmed by analytical reverse-phase high-performance liquid chromatography and matrix-assisted laser-desorption mass-spectrometry ( $m/z$ =2137.1 ((M+H)<sup>+</sup>)).

#### Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) Assay

Representative compounds were serially diluted in dimethyl sulfoxide (DMSO) starting at 50 μM (2× starting concentration; 10% DMSO) and 10 μL were transferred into a 384-well plate. Then 10 μL of a protein/probe/antibody mix was added to each well at final concentrations listed in TABLE 1. The samples are then mixed on a shaker for 1 minute and incubated for an additional 3 hours at room temperature. For each assay, the probe/antibody and protein/probe/antibody were included on each assay plate as negative and positive controls, respectively. Fluorescence was measured on the ENVISION plate reader (Perkin Elmer) using a 340/35 nm excitation filter and 520/525 (F-Bak peptide) and 495/510 nm (Tb-labeled anti-Histidine antibody) emission filters. Dissociation constants ( $K_d$ ) are shown in TABLE 2 below and were determined using Wang's equation (Wang Z.-X. An Exact Mathematical Expression For Describing Competitive Binding Of Two Different Ligands To A Protein Molecule. *FEBS Lett.* 1995, 360:111-4).

TABLE 1

| Protein, Probe And Antibody Used For TR-FRET Assays |  |              |            |             |               |
|---|--|--------------|------------|-------------|---------------|
| Protein   | Probe  | Protein (nM) | Probe (nM) | Antibody    | Antibody (nM) |
| GST-Bcl-2   | F-Bak Peptide Probe<br>Acetyl-GQVGRQLAIIGDK(6-FAM) INR-amide<br>(SEQ ID NO: 1) | 1            | 100        | Tb-anti-GST | 1             |

6-FAM = 6-carboxyfluorescein.; Tb = terbium; GST = glutathione S-transferase

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The samples were then mixed on a shaker for 1 minute and incubated for an additional 3 hours at room temperature. For each assay, the probe/antibody and protein/probe/antibody were included on each assay plate as negative and positive controls, respectively. Fluorescence was measured on the Envision (Perkin Elmer) using a 340/35 nm excitation filter and 520/525 (F-Bak peptide) and 495/510 nm (Tb-labeled anti-Histidine antibody) emission filters.

Inhibition constants ( $K_i$ ) for compounds according to the invention are shown in TABLE 2 below. Where the  $K_i$  for a compound is represented as "<" (less than) a certain numerical value, it is intended to mean that the binding affinity value (e.g., for Bcl-2) is lower than the limit of detection of the assay used. Inhibition constants were determined using Wang's equation (Wang Zx. An Exact Mathematical Expression For Describing Competitive Binding Of Two Different Ligands To A Protein Molecule. *FEBS Lett.* 1995, 360:111-4).

TABLE 2

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 1                                      | 0.000225  |
| 2                                      | <0.000010 |
| 3                                      | 0.000013  |
| 4                                      | <0.000010 |
| 5                                      | <0.000010 |
| 6                                      | 0.000018  |
| 7                                      | 0.00492   |
| 8                                      | 0.000153  |
| 9                                      | <0.000010 |
| 10                                     | <0.000010 |
| 11                                     | 0.000016  |
| 12                                     | <0.000010 |
| 13                                     | <0.000010 |
| 14                                     | 0.002798  |
| 15                                     | <0.000010 |
| 16                                     | 0.000219  |
| 17                                     | 0.00009   |
| 18                                     | 0.000017  |
| 19                                     | 0.000226  |
| 20                                     | 0.000181  |
| 21                                     | 0.000912  |
| 22                                     | 0.000291  |
| 23                                     | 0.000083  |
| 24                                     | <0.000010 |
| 25                                     | <0.000010 |
| 26                                     | 0.000011  |
| 27                                     | 0.000134  |
| 28                                     | <0.000010 |
| 29                                     | <0.000010 |
| 30                                     | <0.000010 |
| 31                                     | <0.000010 |
| 32                                     | <0.000010 |
| 33                                     | <0.000010 |
| 34                                     | 0.00001   |
| 35                                     | <0.000010 |
| 36                                     | 0.000017  |
| 37                                     | <0.000010 |
| 38                                     | 0.0003    |
| 39                                     | 0.000012  |
| 40                                     | <0.000010 |
| 41                                     | <0.000010 |
| 42                                     | 0.000439  |
| 43                                     | 0.000012  |
| 44                                     | <0.000010 |
| 45                                     | <0.000010 |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 46                                     | 0.000935  |
| 47                                     | <0.000010 |
| 48                                     | <0.000010 |
| 49                                     | 0.000074  |
| 50                                     | 0.000021  |
| 51                                     | <0.000010 |
| 52                                     | 0.000114  |
| 53                                     | <0.000010 |
| 54                                     | 0.002071  |
| 55                                     | <0.000010 |
| 56                                     | 0.000037  |
| 57                                     | 0.000063  |
| 58                                     | <0.000010 |
| 59                                     | 0.000203  |
| 60                                     | <0.000010 |
| 61                                     | 0.000091  |
| 62                                     | <0.000010 |
| 63                                     | <0.000010 |
| 64                                     | <0.000010 |
| 65                                     | <0.000010 |
| 66                                     | <0.000010 |
| 67                                     | <0.000010 |
| 68                                     | 0.000012  |
| 69                                     | 0.001157  |
| 70                                     | 0.003964  |
| 71                                     | 0.00001   |
| 72                                     | <0.000010 |
| 73                                     | <0.000010 |
| 74                                     | 0.000029  |
| 75                                     | <0.000010 |
| 76                                     | 0.000196  |
| 77                                     | 0.000213  |
| 78                                     | <0.000010 |
| 79                                     | <0.000010 |
| 80                                     | <0.000010 |
| 81                                     | <0.000010 |
| 82                                     | 0.000328  |
| 83                                     | 0.000071  |
| 84                                     | 0.000123  |
| 85                                     | 0.000391  |
| 86                                     | 0.000498  |
| 87                                     | 0.000618  |
| 88                                     | 0.000672  |
| 89                                     | 0.000073  |
| 90                                     | 0.000013  |
| 91                                     | 0.000487  |
| 92                                     | 0.000128  |
| 93                                     | 0.003461  |
| 94                                     | 0.000678  |
| 95                                     | 0.000014  |
| 96                                     | 0.000014  |
| 97                                     | 0.000017  |
| 98                                     | <0.000010 |
| 99                                     | 0.000233  |
| 100                                    | <0.000010 |
| 101                                    | 0.000021  |
| 102                                    | 0.000094  |
| 103                                    | <0.000010 |
| 104                                    | 0.000016  |
| 105                                    | <0.000010 |
| 106                                    | 0.000895  |
| 107                                    | 0.000035  |
| 108                                    | <0.000010 |
| 109                                    | 0.000127  |
| 110                                    | 0.000557  |
| 111                                    | <0.000010 |
| 112                                    | <0.000010 |
| 113                                    | <0.000010 |
| 114                                    | <0.000010 |
| 115                                    | <0.000010 |
| 116                                    | <0.000010 |
| 117                                    | <0.000010 |
| 118                                    | <0.000010 |
| 119                                    | <0.000010 |
| 120                                    | <0.000010 |
| 121                                    | <0.000010 |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 122                                    | <0.000010 |
| 123                                    | <0.000010 |
| 124                                    | <0.000010 |
| 125                                    | <0.000010 |
| 126                                    | <0.000010 |
| 127                                    | <0.000010 |
| 128                                    | <0.000010 |
| 129                                    | 0.000002  |
| 130                                    | <0.000010 |
| 131                                    | <0.000010 |
| 132                                    | <0.000010 |
| 133                                    | <0.000010 |
| 134                                    | <0.000010 |
| 135                                    | <0.000010 |
| 136                                    | <0.000010 |
| 137                                    | <0.000010 |
| 138                                    | <0.000010 |
| 139                                    | <0.000010 |
| 140                                    | <0.000010 |
| 141                                    | <0.000010 |
| 142                                    | 0.00013   |
| 143                                    | <0.000010 |
| 144                                    | <0.000010 |
| 145                                    | <0.000010 |
| 146                                    | <0.000010 |
| 147                                    | <0.000010 |
| 148                                    | <0.000010 |
| 149                                    | <0.000010 |
| 150                                    | <0.000010 |
| 151                                    | 0.000017  |
| 152                                    | <0.000010 |
| 153                                    | <0.000010 |
| 154                                    | <0.000010 |
| 155                                    | 0.000059  |
| 156                                    | <0.000010 |
| 157                                    | <0.000010 |
| 158                                    | <0.000010 |
| 159                                    | <0.000010 |
| 160                                    | <0.000010 |
| 161                                    | <0.000010 |
| 162                                    | <0.000010 |
| 163                                    | <0.000010 |
| 164                                    | <0.000010 |
| 165                                    | <0.000010 |
| 166                                    | <0.000010 |
| 167                                    | <0.000010 |
| 168                                    | <0.000010 |
| 169                                    | 0.000021  |
| 170                                    | 0.000022  |
| 171                                    | <0.000010 |
| 172                                    | <0.000010 |
| 173                                    | <0.000010 |
| 174                                    | <0.000010 |
| 175                                    | 0.000119  |
| 176                                    | 0.000023  |
| 177                                    | 0.000111  |
| 178                                    | 0.000076  |
| 179                                    | <0.000010 |
| 180                                    | <0.000010 |
| 181                                    | 0.000017  |
| 182                                    | 0.000068  |
| 183                                    | <0.000010 |
| 184                                    | <0.000010 |
| 185                                    | 0.000022  |
| 186                                    | 0.000047  |
| 187                                    | 0.00008   |
| 188                                    | <0.000010 |
| 189                                    | 0.000018  |
| 190                                    | 0.000026  |
| 191                                    | <0.000010 |
| 192                                    | <0.000010 |
| 193                                    | <0.000010 |
| 194                                    | <0.000010 |
| 195                                    | <0.000010 |
| 196                                    | <0.000010 |
| 197                                    | <0.000010 |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 198                                    | <0.000010 |
| 199                                    | <0.000010 |
| 200                                    | <0.000010 |
| 201                                    | 0.000014  |
| 202                                    | <0.000010 |
| 203                                    | <0.000010 |
| 204                                    | <0.000010 |
| 205                                    | <0.000010 |
| 206                                    | 0.000036  |
| 207                                    | 0.00003   |
| 208                                    | 0.000104  |
| 209                                    | <0.000010 |
| 210                                    | 0.000011  |
| 211                                    | 0.000058  |
| 212                                    | 0.0001330 |
| 213                                    | <0.000010 |
| 214                                    | <0.000010 |
| 215                                    | <0.000010 |
| 216                                    | <0.000010 |
| 217                                    | <0.000010 |
| 218                                    | 0.000013  |
| 219                                    | 0.001192  |
| 220                                    | 0.000988  |
| 221                                    | 0.000049  |
| 222                                    | 0.000938  |
| 223                                    | 0.000053  |
| 224                                    | <0.000010 |
| 225                                    | 0.000196  |
| 226                                    | 0.000139  |
| 227                                    | <0.000010 |
| 228                                    | 0.026761  |
| 229                                    | 0.002109  |
| 230                                    | 0.000031  |
| 231                                    | 0.000770  |
| 232                                    | 0.001631  |
| 233                                    | 0.001654  |
| 234                                    | 0.000115  |
| 235                                    | 0.000023  |
| 236                                    | 0.000033  |
| 237                                    | 0.000024  |
| 238                                    | <0.000010 |
| 239                                    | 0.000026  |
| 240                                    | <0.000010 |
| 241                                    | <0.000010 |
| 242                                    | 0.000057  |
| 243                                    | 0.000546  |
| 244                                    | 0.000281  |
| 245                                    | 0.000015  |
| 246                                    | 0.000144  |
| 247                                    | 0.000019  |
| 248                                    | 0.000029  |
| 250                                    | 0.000412  |
| 251                                    | 0.000571  |
| 252                                    | <0.000010 |
| 253                                    | 0.000052  |
| 254                                    | <0.000010 |
| 255                                    | <0.000010 |
| 256                                    | <0.000010 |
| 257                                    | 0.000052  |
| 258                                    | <0.000010 |
| 259                                    | <0.000010 |
| 260                                    | 0.000016  |
| 261                                    | 0.000134  |
| 262                                    | <0.000010 |
| 263                                    | 0.000156  |
| 264                                    | 0.000036  |
| 265                                    | <0.000010 |
| 266                                    | <0.000010 |
| 267                                    | 0.000035  |
| 268                                    | <0.000010 |
| 269                                    | 0.000016  |
| 270                                    | <0.000010 |
| 271                                    | 0.000039  |
| 272                                    | 0.000031  |
| 273                                    | 0.000035  |
| 274                                    | 0.000040  |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |           |
|--|-----------|
| EXAMPLE #                              | $K_i$     |
| 275                                    | <0.000010 |
| 276                                    | <0.000010 |
| 277                                    | <0.000010 |
| 278                                    | 0.000252  |
| 279                                    | 0.000035  |
| 280                                    | 0.000071  |
| 281                                    | 0.000145  |
| 282                                    | <0.000010 |
| 283                                    | <0.000010 |
| 284                                    | 0.000024  |
| 285                                    | <0.000010 |
| 286                                    | <0.000010 |
| 287                                    | 0.000081  |
| 288                                    | 0.000251  |
| 289                                    | 0.000090  |
| 290                                    | <0.000010 |
| 291                                    | <0.000010 |
| 292                                    | 0.000190  |
| 293                                    | 0.000093  |
| 294                                    | 0.000046  |
| 295                                    | <0.000010 |
| 296                                    | 0.000512  |
| 297                                    | 0.000174  |
| 298                                    | <0.000010 |
| 299                                    | 0.000039  |
| 300                                    | 0.001627  |
| 301                                    | 0.002065  |
| 302                                    | 0.000332  |
| 303                                    | 0.000044  |
| 304                                    | nd        |
| 305                                    | 0.000033  |
| 306                                    | 0.002067  |
| 307                                    | 0.000130  |
| 308                                    | 0.000141  |
| 309                                    | 0.000023  |
| 310                                    | 0.000165  |
| 311                                    | <0.000010 |
| 312                                    | <0.000010 |
| 313                                    | 0.001102  |
| 314                                    | 0.000042  |
| 315                                    | 0.000052  |
| 316                                    | 0.000601  |
| 317                                    | <0.000010 |
| 318                                    | <0.000010 |
| 319                                    | <0.000010 |
| 320                                    | <0.000010 |
| 321                                    | <0.000010 |
| 322                                    | <0.000010 |
| 323                                    | 0.000104  |
| 324                                    | <0.000010 |
| 325                                    | <0.000010 |
| 326                                    | <0.000010 |
| 327                                    | <0.000010 |
| 328                                    | <0.000010 |
| 329                                    | 0.000030  |
| 330                                    | <0.000010 |
| 331                                    | 0.001086  |
| 332                                    | 0.000621  |
| 333                                    | 0.000511  |
| 334                                    | 0.000572  |
| 335                                    | 0.000150  |
| 336                                    | 0.000198  |
| 337                                    | <0.000010 |
| 338                                    | 0.000013  |
| 339                                    | 0.000036  |
| 340                                    | <0.000010 |
| 341                                    | <0.000010 |
| 342                                    | <0.000010 |
| 343                                    | <0.000010 |
| 344                                    | <0.000010 |
| 345                                    | <0.000010 |
| 346                                    | 0.000042  |
| 347                                    | 0.000013  |
| 348                                    | 0.000034  |
| 349                                    | 0.000023  |
| 350                                    | <0.000010 |

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TABLE 2-continued

| TR-FRET Bcl-2 Binding $K_i$ ( $\mu$ M) |            |
|--|------------|
| EXAMPLE #                              | $K_i$      |
| 351                                    | <0.000010  |
| 352                                    | 0.000014   |
| 353                                    | <0.000010  |
| 354                                    | 0.000010   |
| 355                                    | 0.000014   |
| 356                                    | 0.000039   |
| 357                                    | <0.000010  |
| 358                                    | <0.000010  |
| 359                                    | <0.000010  |
| 360                                    | <0.000010  |
| 361                                    | <0.000010  |
| 362                                    | 0.000016   |
| 363                                    | 0.000017   |
| 364                                    | <0.000010  |
| 365                                    | <0.000010  |
| 366                                    | 0.000024   |
| 367                                    | nd         |
| 368                                    | nd         |
| 369                                    | <0.000010  |
| 370                                    | 0.000285   |
| 371                                    | <0.0000010 |
| 372                                    | nd         |
| 373                                    | <0.0000010 |
| 374                                    | <0.0000010 |
| 375                                    | 0.00010999 |
| 376                                    | <0.0000010 |
| 377                                    | <0.0000010 |
| 378                                    | <0.0000010 |

nd = not determined

The inhibition constant ( $K_i$ ) is the dissociation constant of an enzyme-inhibitor complex or a protein/small molecule complex, wherein the small molecule is inhibiting binding of one protein to another protein or peptide. So a large  $K_i$  value indicates a low binding affinity and a small  $K_i$  value indicates a high binding affinity.

TABLE 2 shows inhibition constants for the inhibition of a Bak BH3 peptide probe to Bcl-2 protein and indicate that compounds according to the invention have high binding affinities for anti-apoptotic Bcl-2 protein. The compounds are therefore expected to have utility in treatment of diseases during which anti-apoptotic Bcl-2 protein is expressed.

## RS4; 11 Cell Viability Assay

The acute lymphoblastic leukemia (ALL) cell line RS4; 11 was used as the primary human cell line to assess the cellular activity of Bcl-2 selective agents in vitro and their efficacy in vivo. Previous studies have shown by BH3 profiling, a mitochondrial assay that classifies blocks in the intrinsic apoptotic pathway, that RS4; 11 cells were highly dependant on BCL-2 for survival and sensitive to the Bcl-2 family member inhibitor ABT-737 (Blood, 2008, Vol. 111, 2300-2309). The prevalence of Bcl-2 complexed to the proapoptotic BH3 protein Bim in RS4; 11 suggests that these cells are "primed" or more susceptible to cell death by antagonism of the antiapoptotic protein Bcl-2 for which they depend on for survival.



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RS4; 11 cells were cultured in RPMI-1640 supplemented with 2 mM L-glutamine, 10% FBS, 1 mM sodium pyruvate, 2 mM HEPES, 1% penicillin/streptomycin (Invitrogen), 4.5 g/L glucose and maintained at 37 C containing 5% CO<sub>2</sub>. To test for the cellular activity of compounds in vitro, cells were treated at 50,000 cells per well in 96-well microtiter plates in the presence of 10% human serum for 48 hours in a humidified chamber with 5% CO<sub>2</sub>. Cell cytotoxicity EC<sub>50</sub> values were assessed using CellTiter Glo (Promega) according to the manufacturer's recommendations. The EC<sub>50</sub> values were determined as a percentage of viable cells following treatment compared to the untreated control cells.

TABLE 3

| RS4;11 EC <sub>50</sub> Values (μM) |         |
|-------------------------------------|---------|
| EXAMPLE #                           | EC50    |
| 1                                   | 0.712   |
| 2                                   | 0.783   |
| 3                                   | 0.0142  |
| 4                                   | 0.01854 |
| 5                                   | 0.01241 |
| 6                                   | 0.03487 |
| 7                                   | 0.192   |
| 8                                   | 0.158   |
| 9                                   | 0.01476 |
| 10                                  | 0.05202 |
| 11                                  | 0.01393 |
| 12                                  | 0.03471 |
| 13                                  | 0.0232  |
| 14                                  | 3.8947  |
| 15                                  | 0.01276 |
| 16                                  | 1.2098  |
| 17                                  | 0.475   |
| 18                                  | 0.086   |
| 19                                  | 0.465   |
| 20                                  | 0.191   |
| 21                                  | 0.062   |
| 22                                  | 0.085   |
| 23                                  | 0.045   |
| 24                                  | 0.00983 |
| 25                                  | 0.007   |
| 26                                  | 0.05888 |
| 27                                  | 0.33237 |
| 28                                  | 0.0419  |
| 29                                  | 0.02047 |
| 30                                  | 0.01529 |
| 31                                  | 0.01565 |
| 32                                  | 0.08147 |
| 33                                  | 0.00711 |
| 34                                  | 0.00748 |
| 35                                  | 0.29147 |
| 36                                  | 0.18137 |
| 37                                  | 0.00118 |
| 38                                  | 3.5092  |
| 39                                  | 0.01974 |
| 40                                  | 0.09974 |
| 41                                  | 0.05801 |
| 42                                  | 0.53412 |
| 43                                  | 0.27208 |
| 44                                  | 0.05309 |
| 45                                  | 0.00992 |
| 46                                  | >5      |
| 47                                  | 0.03265 |
| 48                                  | 0.00333 |
| 49                                  | 0.35161 |
| 50                                  | 0.31264 |
| 51                                  | 0.02308 |
| 52                                  | 0.19964 |
| 53                                  | 0.06674 |
| 54                                  | 1.9158  |
| 55                                  | 0.0132  |

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TABLE 3-continued

| RS4;11 EC <sub>50</sub> Values (μM) |         |
|-------------------------------------|---------|
| EXAMPLE #                           | EC50    |
| 56                                  | 0.08654 |
| 57                                  | 0.42611 |
| 58                                  | >5      |
| 59                                  | 0.7215  |
| 60                                  | 0.05948 |
| 61                                  | 0.18337 |
| 62                                  | 0.02506 |
| 63                                  | 0.00751 |
| 64                                  | 0.00025 |
| 65                                  | 0.00025 |
| 66                                  | 0.01893 |
| 67                                  | 0.04954 |
| 68                                  | 0.10846 |
| 69                                  | 1.7243  |
| 70                                  | >5      |
| 71                                  | 0.09165 |
| 72                                  | 0.00751 |
| 73                                  | 0.02369 |
| 74                                  | 0.057   |
| 75                                  | 0.01509 |
| 76                                  | 0.51131 |
| 77                                  | 0.76196 |
| 78                                  | 0.01252 |
| 79                                  | 0.0649  |
| 80                                  | 0.06863 |
| 81                                  | 0.04814 |
| 82                                  | 0.68383 |
| 83                                  | 0.197   |
| 84                                  | 0.158   |
| 85                                  | 1.95    |
| 86                                  | 1.02    |
| 87                                  | 1.18    |
| 88                                  | 0.447   |
| 89                                  | 0.06446 |
| 90                                  | 0.06299 |
| 91                                  | 0.18296 |
| 92                                  | 0.08089 |
| 93                                  | >5      |
| 94                                  | 1.6946  |
| 95                                  | 0.02954 |
| 96                                  | 0.04356 |
| 97                                  | 0.05557 |
| 98                                  | 0.0229  |
| 99                                  | 1.3923  |
| 100                                 | 0.13666 |
| 101                                 | 0.2991  |
| 102                                 | 0.62178 |
| 103                                 | 0.03917 |
| 104                                 | 0.07125 |
| 105                                 | 0.05357 |
| 106                                 | 0.82639 |
| 107                                 | 0.06117 |
| 108                                 | 0.02407 |
| 109                                 | 0.18339 |
| 110                                 | 0.53638 |
| 111                                 | 0.01451 |
| 112                                 | 0.02063 |
| 113                                 | 0.00136 |
| 114                                 | 0.01078 |
| 115                                 | 0.01184 |
| 116                                 | 0.02853 |
| 117                                 | 0.0182  |
| 118                                 | 0.01294 |
| 119                                 | 0.01138 |
| 120                                 | 0.00147 |
| 121                                 | 0.05972 |
| 122                                 | 0.00185 |
| 123                                 | 0.00333 |
| 124                                 | 0.21224 |
| 125                                 | 0.00838 |
| 126                                 | 0.05359 |
| 127                                 | 0.00975 |
| 128                                 | 0.00589 |
| 129                                 | 0.01484 |
| 130                                 | 0.01059 |
| 131                                 | 0.01266 |

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TABLE 3-continued

| RS4;11 EC <sub>50</sub> Values (uM) |         |
|-------------------------------------|---------|
| EXAMPLE #                           | EC50    |
| 132                                 | 0.02209 |
| 133                                 | 0.03186 |
| 134                                 | 0.00251 |
| 135                                 | 0.00237 |
| 136                                 | 0.00296 |
| 137                                 | 0.01272 |
| 138                                 | 0.00152 |
| 139                                 | 0.01681 |
| 140                                 | 0.01275 |
| 141                                 | 0.02044 |
| 142                                 | 0.34531 |
| 143                                 | 0.01914 |
| 144                                 | 0.0212  |
| 145                                 | 0.004   |
| 146                                 | 0.01916 |
| 147                                 | 0.02618 |
| 148                                 | 0.00938 |
| 149                                 | 0.01347 |
| 150                                 | 0.05103 |
| 151                                 | 0.03372 |
| 152                                 | 0.02037 |
| 153                                 | 0.01723 |
| 154                                 | 0.02647 |
| 155                                 | 0.59421 |
| 156                                 | 0.00805 |
| 157                                 | 0.01086 |
| 158                                 | 0.01793 |
| 159                                 | 0.01179 |
| 160                                 | 0.08363 |
| 161                                 | 0.03465 |
| 162                                 | 0.01297 |
| 163                                 | 0.00432 |
| 164                                 | 0.01476 |
| 165                                 | 0.0051  |
| 166                                 | 0.01185 |
| 167                                 | 0.00093 |
| 168                                 | 0.08867 |
| 169                                 | 0.07626 |
| 170                                 | 0.12515 |
| 171                                 | 0.05272 |
| 172                                 | 0.02053 |
| 173                                 | 0.00516 |
| 174                                 | 0.12621 |
| 175                                 | >1      |
| 176                                 | 0.13353 |
| 177                                 | 0.15936 |
| 178                                 | 0.20234 |
| 179                                 | 0.04273 |
| 180                                 | 0.0118  |
| 181                                 | 0.10612 |
| 182                                 | 0.1234  |
| 183                                 | 0.01753 |
| 184                                 | 0.02323 |
| 185                                 | 0.02747 |
| 186                                 | 0.06443 |
| 187                                 | 0.21494 |
| 188                                 | 0.01638 |
| 189                                 | 0.14397 |
| 190                                 | 0.55068 |
| 191                                 | 0.00691 |
| 192                                 | 0.00241 |
| 193                                 | 0.00076 |
| 194                                 | 0.00819 |
| 195                                 | 0.00207 |
| 196                                 | 0.00172 |
| 197                                 | 0.0125  |
| 198                                 | 0.03619 |
| 199                                 | 0.00506 |
| 200                                 | 0.01099 |
| 201                                 | 0.59132 |
| 202                                 | 0.0438  |
| 203                                 | 0.02208 |
| 204                                 | 0.16475 |
| 205                                 | 0.01059 |
| 206                                 | 0.05291 |
| 207                                 | 0.00376 |

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TABLE 3-continued

| RS4;11 EC <sub>50</sub> Values (uM) |            |
|-------------------------------------|------------|
| EXAMPLE #                           | EC50       |
| 208                                 | 0.12121    |
| 209                                 | 0.0045     |
| 210                                 | 0.06022    |
| 211                                 | 0.3073     |
| 212                                 | 0.01283    |
| 213                                 | 0.0060976  |
| 214                                 | 0.0043751  |
| 215                                 | 0.00056038 |
| 216                                 | 0.68263    |
| 217                                 | 0.0015528  |
| 218                                 | 0.0072907  |
| 219                                 | >1         |
| 220                                 | >1         |
| 221                                 | 0.094771   |
| 222                                 | >1         |
| 223                                 | 0.18208    |
| 224                                 | 0.013887   |
| 225                                 | 0.56001    |
| 226                                 | 0.1178     |
| 227                                 | 0.0073566  |
| 228                                 | >1         |
| 229                                 | >1         |
| 230                                 | 0.052821   |
| 231                                 | 0.52301    |
| 232                                 | >1         |
| 233                                 | >1         |
| 234                                 | 0.13532    |
| 235                                 | 0.03232    |
| 236                                 | 0.04292    |
| 237                                 | 0.05316    |
| 238                                 | 0.10303    |
| 239                                 | 0.023699   |
| 240                                 | 0.017266   |
| 241                                 | 0.11377    |
| 242                                 | 0.22275    |
| 243                                 | 0.80718    |
| 244                                 | 0.79378    |
| 245                                 | 0.083614   |
| 246                                 | 0.40218    |
| 247                                 | 0.092976   |
| 248                                 | 0.099588   |
| 250                                 | >1         |
| 251                                 | 0.91782    |
| 252                                 | 0.003475   |
| 253                                 | 0.049586   |
| 254                                 | 0.019908   |
| 255                                 | 0.009004   |
| 256                                 | 0.017997   |
| 257                                 | 0.026002   |
| 258                                 | 0.00055345 |
| 259                                 | 0.00038795 |
| 260                                 | 0.0054323  |
| 261                                 | 0.18366    |
| 262                                 | 0.016346   |
| 263                                 | >1         |
| 264                                 | 0.68866    |
| 265                                 | 0.0071718  |
| 266                                 | 0.0072924  |
| 267                                 | 0.06944    |
| 268                                 | 0.048792   |
| 269                                 | 0.0072346  |
| 270                                 | 0.0025216  |
| 271                                 | 0.43657    |
| 272                                 | 0.84006    |
| 273                                 | 0.20925    |
| 274                                 | 0.21418    |
| 275                                 | 0.14303    |
| 276                                 | 0.0035006  |
| 277                                 | 0.0081845  |
| 278                                 | 0.79393    |
| 279                                 | 0.22492    |
| 280                                 | 0.45923    |
| 281                                 | 0.65371    |
| 282                                 | 0.032187   |
| 283                                 | 0.013096   |
| 284                                 | 0.16213    |

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TABLE 3-continued

| RS4;11 EC <sub>50</sub> Values (μM) |           |
|-------------------------------------|-----------|
| EXAMPLE #                           | EC50      |
| 285                                 | 0.057413  |
| 286                                 | 0.034464  |
| 287                                 | 0.59312   |
| 288                                 | 0.39042   |
| 289                                 | 0.6687    |
| 290                                 | 0.10663   |
| 291                                 | 0.016079  |
| 292                                 | 0.88938   |
| 293                                 | 0.28715   |
| 294                                 | 0.12525   |
| 295                                 | 0.014803  |
| 296                                 | 0.76869   |
| 297                                 | 0.59157   |
| 298                                 | 0.070305  |
| 299                                 | 0.067981  |
| 300                                 | 0.76334   |
| 301                                 | >1        |
| 302                                 | 0.38106   |
| 303                                 | 0.04776   |
| 304                                 | 0.29755   |
| 305                                 | 0.032539  |
| 306                                 | 0.55348   |
| 307                                 | 0.12767   |
| 308                                 | 0.257     |
| 309                                 | 0.052421  |
| 310                                 | >1        |
| 311                                 | 0.035835  |
| 312                                 | 0.016178  |
| 313                                 | >1        |
| 314                                 | 0.66006   |
| 315                                 | 0.21027   |
| 316                                 | >1        |
| 317                                 | 0.013313  |
| 318                                 | 0.011566  |
| 319                                 | 0.0044972 |
| 320                                 | 0.050974  |
| 321                                 | 0.0188    |
| 322                                 | 0.012367  |
| 323                                 | 0.71689   |
| 324                                 | 0.0045254 |
| 325                                 | 0.012319  |
| 326                                 | 0.023133  |
| 327                                 | 0.0027224 |
| 328                                 | 0.0098808 |
| 329                                 | 0.42369   |
| 330                                 | 0.0097843 |
| 331                                 | 0.92638   |
| 332                                 | 0.45738   |
| 333                                 | 0.46292   |
| 334                                 | >1        |
| 335                                 | 0.26951   |
| 336                                 | 0.35134   |
| 337                                 | 0.001759  |
| 338                                 | 0.003399  |
| 339                                 | 0.45016   |
| 340                                 | 0.05646   |
| 341                                 | 0.031652  |
| 342                                 | 0.050891  |
| 343                                 | 0.12664   |
| 344                                 | 0.0066616 |
| 345                                 | 0.0092536 |
| 346                                 | 0.19003   |
| 347                                 | 0.018849  |
| 348                                 | 0.050263  |
| 349                                 | 0.023086  |
| 350                                 | 0.0058378 |
| 351                                 | 0.0020618 |
| 352                                 | 0.0011961 |
| 353                                 | 0.0050512 |
| 354                                 | 0.053231  |
| 355                                 | 0.018771  |
| 356                                 | 0.026623  |
| 357                                 | 0.013235  |
| 358                                 | 0.0038131 |
| 359                                 | 0.0059243 |
| 360                                 | 0.0098968 |

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TABLE 3-continued

| RS4;11 EC <sub>50</sub> Values (μM) |            |
|-------------------------------------|------------|
| EXAMPLE #                           | EC50       |
| 361                                 | 0.00053755 |
| 362                                 | 0.031726   |
| 363                                 | 0.02643    |
| 364                                 | 0.011244   |
| 365                                 | 0.0030168  |
| 366                                 | 0.016548   |
| 367                                 | nd         |
| 368                                 | nd         |
| 369                                 | 0.0079974  |
| 370                                 | nd         |
| 371                                 | 0.007165   |
| 372                                 | nd         |
| 373                                 | nd         |
| 374                                 | 0.015475   |
| 375                                 | 0.56013    |
| 376                                 | 0.008765   |
| 377                                 | 0.002377   |
| 378                                 | 0.006764   |

nd = not determined

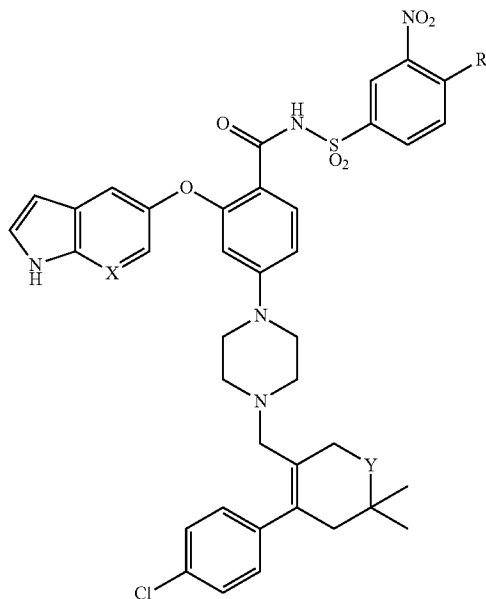
TABLE 3 shows the utility of compounds having Formula I to functionally inhibit anti-apoptotic Bcl-2 protein in a cellular context. The acute lymphoblastic leukemia (ALL) cell line RS4; 11 has been shown by BH3 profiling, a mitochondrial assay that classifies blocks in the intrinsic apoptotic pathway, to be highly dependant on Bcl-2 for survival and is sensitive to the Bcl-2 family member inhibitor ABT-737 (*Blood*, 2008, Vol. 111, 2300-2309). The ability of compounds to kill RS4; 11 cells is a direct measure of the compounds ability to inhibit anti-apoptotic Bcl-2 protein function. Compounds of Formula I are very effective in killing RS4; 11 cells as demonstrated by low EC<sub>50</sub> values.

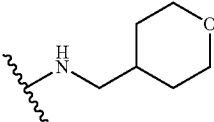
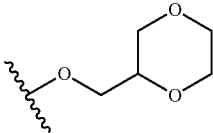
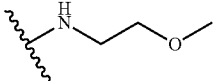
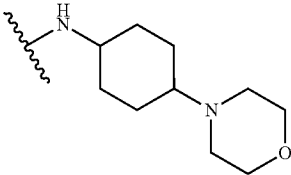
Compounds taught in U.S. patent application Ser. No. 12/631,404, entitled "BCL-2-SELECTIVE APOPTOSIS-INDUCING AGENTS FOR THE TREATMENT OF CANCER AND IMMUNE DISEASES," filed on Dec. 4, 2009, have utility for the treatment of various cancers and autoimmune diseases due to their activity against Bcl-2 family proteins, and more specifically Bcl-2. These compounds bind to Bcl-2 with high affinity in a FRET based assay described in Ser. No. 12/631,404. The administration of a one or more of these compounds to cells that are dependant on Bcl-2 or Bcl-2 family proteins for survival, such as the RS4;11 B-cell leukemia human tumor cell line, results in apoptosis, also known as programmed cell death. The amount of apoptosis caused by administration of the compound is represented by the EC50 in the cell viability assay, which is a measure of the number of living cells after administration of compound.

TABLE 4 identifies certain compounds (described below in Examples in 19, 20, 23 and 92 and described more fully in Ser. No. 12/631,404, the disclosure of which is incorporated herein by reference) with the various substituents being defined by R, X and Y as set forth. As can be seen from TABLE 4, these compounds exhibit a trend of increasing binding affinity (K<sub>i</sub>) for Bcl-2 with increasing levels of apoptosis, or cell death, in the Bcl-2 dependant tumor cell line RS4; 11. On this basis, the inventors expect that compounds with even greater affinity towards Bcl-2 than those compounds shown in Table 4 will exhibit a similar trend, potentially eliciting even greater levels of apoptosis, when administered to cells dependent on Bcl-2 for survival.

TABLE 4

Selected compounds in U.S. patent application No. 12/631,404



| EXAMPLE | R   | X | Y | Bcl-2 FRET<br>$K_f$ ( $\mu\text{M}$ ) | RS4; 11 EC50<br>( $\mu\text{M}$ ) |
|---------|---|---|---|---------------------------------------|-----------------------------------|
| (23)    |   | C | O | 0.000083                              | 0.045                             |
| (92)    |  | C | C | 0.000128                              | 0.081                             |
| (20)    |  | C | C | 0.000181                              | 0.191                             |
| (19)    |  | C | C | 0.000226                              | 0.465                             |

To this end, binding affinity and cellular activity for compounds according to the present invention were compared with structurally similar indole compounds. In particular, the compounds of the present invention, in which a nitrogen is contained at a specific position within the heteroarene fused to the heteroaryl ring were compared with the corresponding indole compounds, which latter compounds lack only the specific nitrogen substitution included in the compounds of the present invention.

As can be seen in TABLE 5, compounds of the present invention having the specific nitrogen substitutions shown (i.e., compounds of Examples 1, 2, 3, 4, 5, 6, 9, 10, 11, 12, 13, 15, 16, and 17, where Z=N) in fact achieve relatively greater

levels of apoptosis when administered to cells that depend on Bcl-2 for survival and have increased affinity towards Bcl-2 relative to the corresponding structural analogs lacking the specific nitrogen substitution (i.e., compounds of Examples 87, 88, 89, 90, 91, 19, 20, 21, 92, 22, 23, 93, and 94, respectively, where  $Z=C$ , taught in 9696USL2, the disclosure of which is incorporated herein by reference).

Specifically, the seventh column of TABLE 5 compares binding affinity of compounds of the present invention (the compound identified by the designated substituents in the uppermost row in each pair of rows set apart by blank rows) to corresponding compounds lacking the described nitrogen substitution. In each comparison, compounds of the present



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application (upper row of each pair of rows separated by a blank row) bind Bcl-2 with greater affinity to Bcl-2 than the corresponding analogs (lower row of each pair of rows separated by a blank row).

Further, column 8 of TABLE 5 compares the amount of apoptosis in the Bcl-2 dependant RS4; 11 cell line achieved using compounds of the present invention (again the compound identified by the designated substituents in the uppermost row in each pair of rows set apart by blank rows) to that achieved using compounds of Examples 87, 88, 89, 90, 91, 19, 20, 21, 92, 22, 23, 93, and 94, where Z=C. In each comparison, compounds of the present invention (upper row of each pair of rows separated by a blank row) achieve greater extent of apoptosis in Bcl-2 dependent RS4; 11 cells than the corresponding analogs (lower row of each pair of rows separated by a blank row).

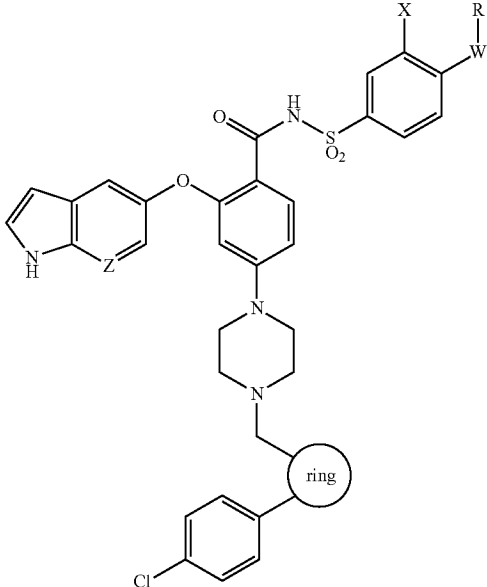
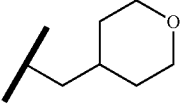
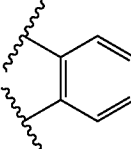
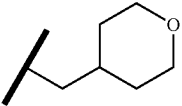
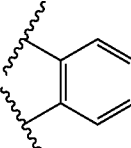
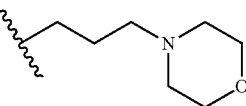
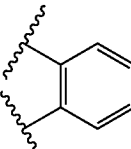
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The increase in binding affinity between the compounds of the present invention and corresponding analogs ranges from 2.7× to greater than 100×, and the increased potency in RS4; 11 cells ranges from a 1.65× increase to greater than 10× increase.

As detailed below, a specific substitution of a nitrogen atom for a carbon atom leads to unexpected increase in binding affinity to antiapoptotic Bcl-2 and increase in potency in cell viability assays assessing apoptosis in Bcl-2 dependent cell lines.

This invention therefore comprises a series of compounds that demonstrate unexpected properties with respect to their binding to and inhibiting the activity of anti-apoptotic Bcl-2 protein to a significantly greater extent than corresponding analog compounds.

TABLE 5

| Direct comparison of compounds of the present invention with corresponding analogs. |   |    |                 |  |   |                       |                      |  |
|---|---|----|-----------------|--|---|-----------------------|----------------------|--|
|  |   |    |                 |  |   |                       |                      |  |
| EXAMPLE   | R   | W  | X               | Ring   | Z | Bcl-2 FRET<br>ki (μM) | RS4; 11<br>EC50 (μM) |  |
| (1)   |  | NH | NO <sub>2</sub> |  | N | 0.000225              | 0.712                |  |
| (87)  |  | NH | NO <sub>2</sub> |  | C | 0.000618              | 1.180                |  |
| (2)   |  | NH | NO <sub>2</sub> |  | N | <0.000010             | 0.783                |  |

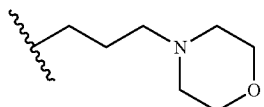
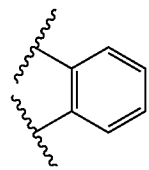
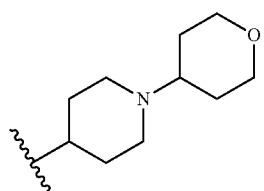
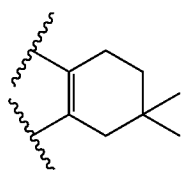
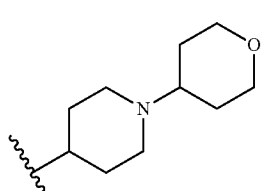
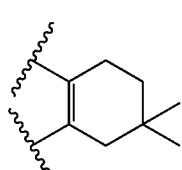
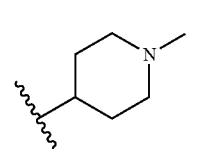
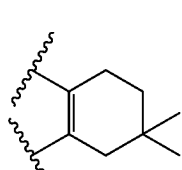
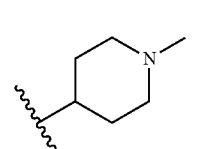
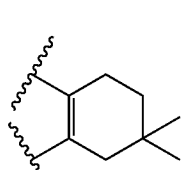
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TABLE 5-continued

Direct comparison of compounds of the present invention with corresponding analogs.

| EXAMPLE | R   | W  | X               | Ring  | Z | Bcl-2 FRET<br>ki (μM) | RS4; 11<br>EC50 (μM) |
|---------|---|----|-----------------|---|---|-----------------------|----------------------|
| (88)    |   | NH | NO <sub>2</sub> |   | C | 0.672                 | 0.447                |
| (3)     |  | NH | NO <sub>2</sub> |  | N | 0.000013              | 0.0142               |
| (89)    |  | NH | NO <sub>2</sub> |  | C | 0.000074              | 0.064                |
| (4)     |  | NH | NO <sub>2</sub> |  | N | <0.00001              | 0.019                |
| (90)    |  | NH | NO <sub>2</sub> |  | C | 0.000013              | 0.063                |

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TABLE 5-continued

Direct comparison of compounds of the present invention with corresponding analogs.

| <div></div> |             |    |                 |             |   |                       |                      |
|-------------|-------------|----|-----------------|-------------|---|-----------------------|----------------------|
| EXAMPLE     | R           | W  | X               | Ring        | Z | Bcl-2 FRET<br>ki (μM) | RS4; 11<br>EC50 (μM) |
| (5)         | <div></div> | NH | NO <sub>2</sub> | <div></div> | N | <0.00001              | 0.012                |
| (18)        | <div></div> | NH | NO <sub>2</sub> | <div></div> | C | 0.000017              | 0.086                |
| (6)         | <div></div> | NH | NO <sub>2</sub> | <div></div> | N | 0.000018              | 0.035                |
| (91)        | <div></div> | NH | NO <sub>2</sub> | <div></div> | C | 0.000487              | 0.183                |
| (9)         | <div></div> | NH | NO <sub>2</sub> | <div></div> | N | <0.00001              | 0.015                |

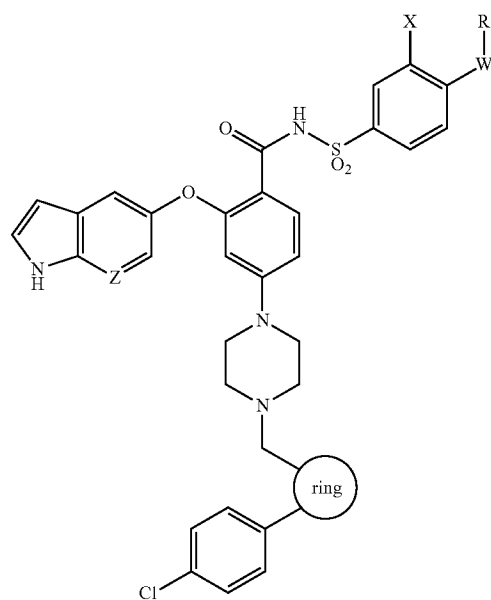
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TABLE 5-continued

Direct comparison of compounds of the present invention with corresponding analogs.



| EXAMPLE | R | W  | X               | Ring | Z | Bcl-2 FRET<br>ki (μM) | RS4; 11<br>EC50 (μM) |
|---------|---|----|-----------------|------|---|-----------------------|----------------------|
| (19)    |   | NH | NO <sub>2</sub> |      | C | 0.000226              | 0.465                |
| (10)    |   | NH | NO <sub>2</sub> |      | N | <0.00001              | 0.052                |
| (20)    |   | NH | NO <sub>2</sub> |      | C | 0.000181              | 0.191                |
| (11)    |   | NH | NO <sub>2</sub> |      | N | 0.000016              | 0.014                |
| (21)    |   | NH | NO <sub>2</sub> |      | C | 0.000912              | 0.062                |



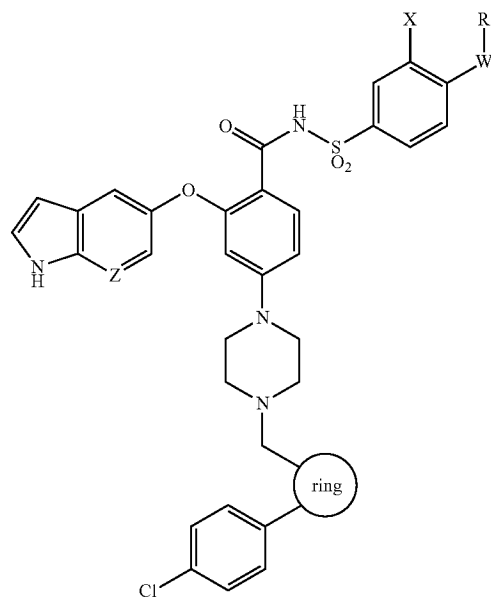
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TABLE 5-continued

Direct comparison of compounds of the present invention with corresponding analogs.



| EXAMPLE | R | W  | X               | Ring | Z | Bcl-2 FRET<br>ki (μM) | RS4; 11<br>EC50 (μM) |
|---------|---|----|-----------------|------|---|-----------------------|----------------------|
| (12)    |   | O  | NO <sub>2</sub> |      | N | <0.00001              | 0.035                |
| (92)    |   | O  | NO <sub>2</sub> |      | C | 0.000128              | 0.081                |
| (13)    |   | NH | NO <sub>2</sub> |      | N | <0.00001              | 0.023                |
| (22)    |   | NH | NO <sub>2</sub> |      | C | 0.000291              | 0.085                |
| (15)    |   | NH | NO <sub>2</sub> |      | N | <0.00001              | 0.013                |

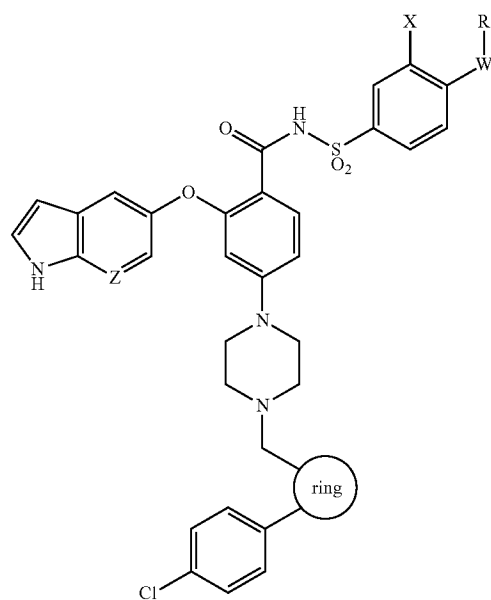
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TABLE 5-continued

Direct comparison of compounds of the present invention with corresponding analogs.

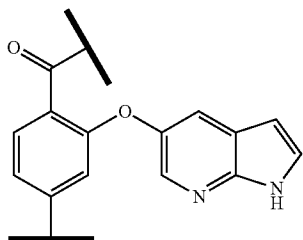


| EXAMPLE | R | W  | X                               | Ring | Z | Bcl-2 FRET<br>ki (μM) | RS4; 11<br>EC50 (μM) |
|---------|---|----|---------------------------------|------|---|-----------------------|----------------------|
| (23)    |   | NH | NO <sub>2</sub>                 |      | C | 0.000083              | 0.045                |
| (16)    |   | NH | SO <sub>2</sub> CF <sub>3</sub> |      | N | 0.000219              | 1.210                |
| (93)    |   | NH | SO <sub>2</sub> CF <sub>3</sub> |      | C | 0.035                 | >5.000               |
| (17)    |   | NH | SO <sub>2</sub> CF <sub>3</sub> |      | N | 0.000090              | 0.475                |
| (94)    |   | NH | SO <sub>2</sub> CF <sub>3</sub> |      | C | 0.000678              | 1.690                |

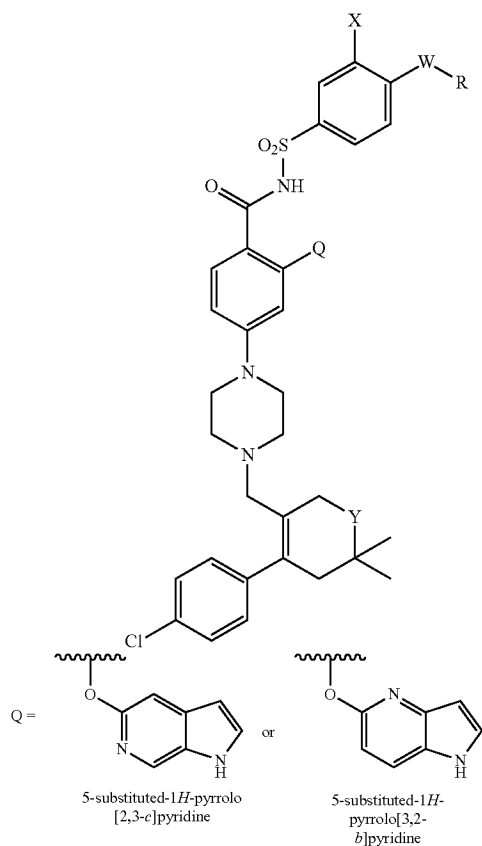
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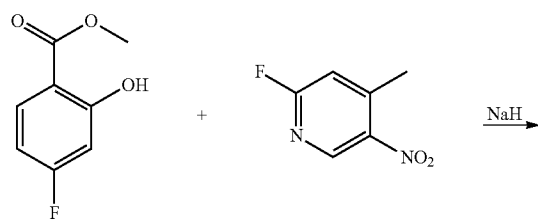
More specifically, compounds of the present invention contain a substitution pattern shown in the diagram below.



Other compounds that contain isomeric ring systems to that shown above, such as those rings systems containing a nitrogen adjacent to the oxygenated carbon within the ring, as shown below, are compromised by instability.

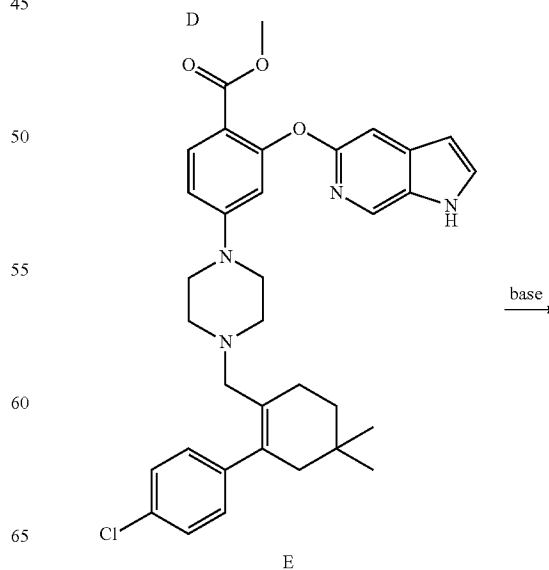
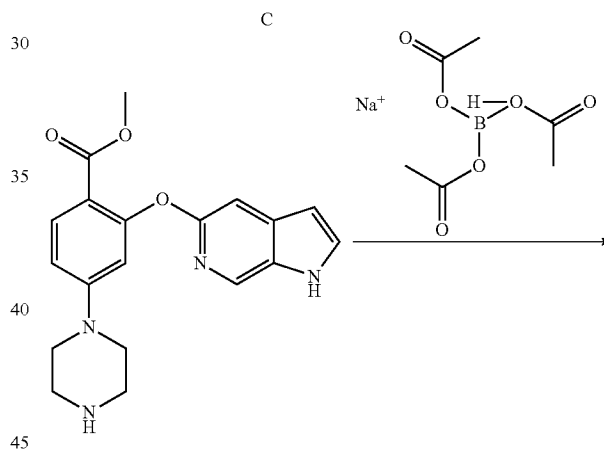
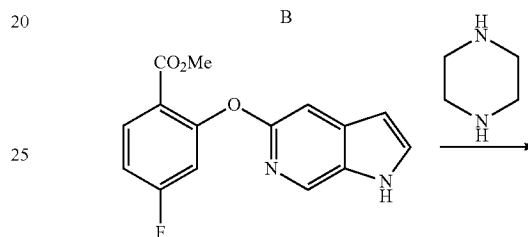
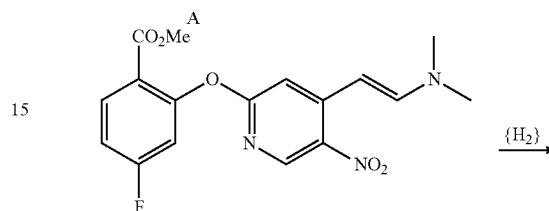
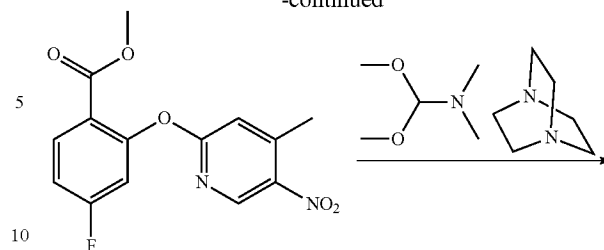


Specifically, this was discovered by the inventors in the following compound preparation. The intermediate structure F, that directly precedes the final product of the unstable compound, was prepared according to the route below. All intermediates A-F were stable and isolable using techniques 55 known to those skilled in the art.

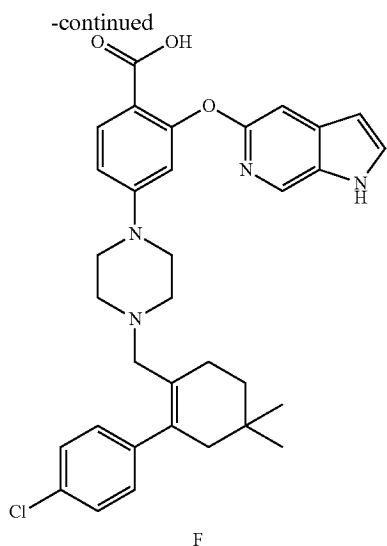


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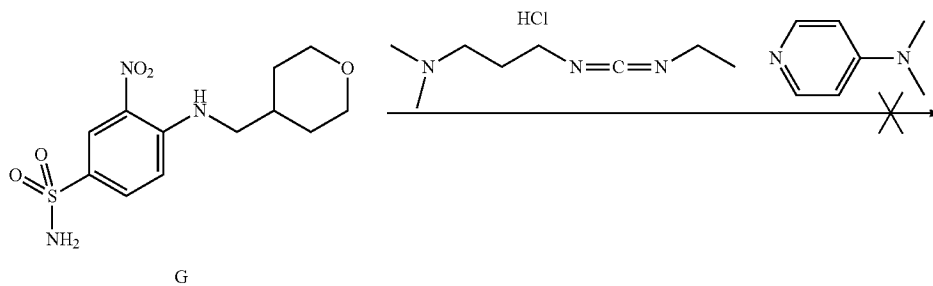
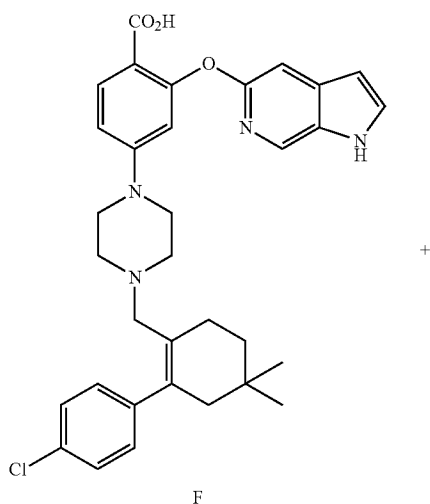
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Intermediate F, shown in the scheme above, was reacted with intermediate G using standard coupling conditions that are known to those skilled in the art. The reaction mixture was analyzed via HPLC/MS to monitor the formation of a peak corresponding to the compound H. While this peak formed within hours of initiating the reaction below, the peak progressively disappeared during workup and chromatography, until it no longer was present. The lack of stability of the putative compound originates from the position of the nitrogen within the fused ring-system described above. This position, which is adjacent to the oxygen-bearing carbon in the 5-substituted-1H-pyrrolo[2,3-c]pyridine ring system shown below and described above, makes the compound H unstable.



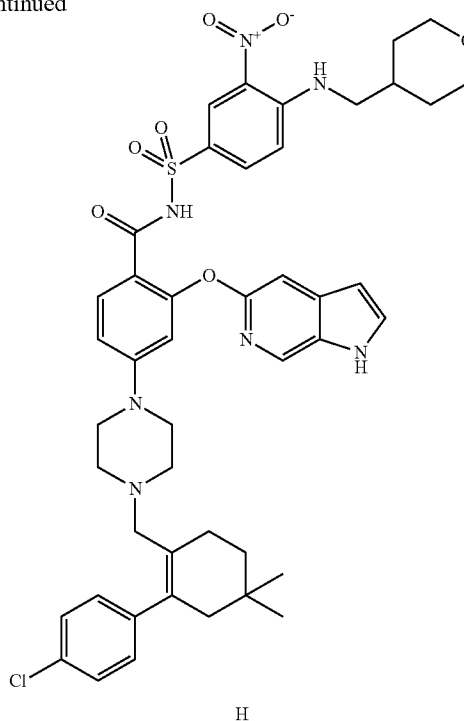


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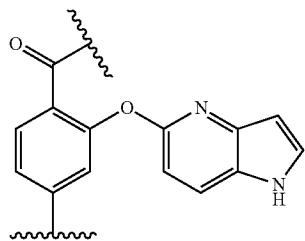
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It is expected that a compound containing the fused 5-substituted-1H-pyrrolo[3,2-b]pyridine ring system below would be similarly unstable, since the position of the nitrogen is adjacent to the oxygen-bearing carbon within the ring.



Therefore, compounds with the 5-substituted-1H-pyrrolo [2,3-b]pyridines are preferred over the isomeric compounds.

It is expected that, because compounds having Formula (I) bind to Bcl-2, they would also have utility as binders to anti-apoptotic proteins having close structural homology to Bcl-2, such as, for example, anti-apoptotic Bcl-X<sub>L</sub>, Bcl-w, Mcl-1 and Bfl-1/A1 proteins.

Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer spleen cancer, and the like is described in commonly-owned PCT US 2004/36770, published as WO 2005/049593, and PCT US 2004/37911, published as WO 2005/024636.

Involvement of Bcl-2 proteins in immune and autoimmune diseases is described in *Current Allergy and Asthma Reports*

2003, 3, 378-384; *British Journal of Haematology* 2000, 110(3), 584-90; *Blood* 2000, 95(4), 1283-92; and *New England Journal of Medicine* 2004, 351(14), 1409-1418.

Involvement of Bcl-2 proteins in arthritis is disclosed in commonly-owned U.S. Provisional Patent Application Ser. No. 60/988,479.

Involvement of Bcl-2 proteins in bone marrow transplant rejection is disclosed in commonly-owned U.S. patent application Ser. No. 11/941,196.

Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system. Cancers include, but are not limited to, hematologic and solid tumor types such as acoustic neuroma, acute leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer (including estrogen-receptor positive breast cancer), bronchogenic carcinoma, Burkitt's lymphoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, gastric carcinoma, germ cell testicular cancer, gestational trophoblastic disease, glioblastoma, head and neck cancer, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer (including small cell

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lung cancer and non-small cell lung cancer), lymphangioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (lymphoma, including diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, peripheral T-cell lymphoma, pinealoma, polycythemia vera, prostate cancer (including hormone-insensitive (refractory) prostate cancer), rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), stomach cancer, squamous cell carcinoma, synovialoma, sweat gland carcinoma, testicular cancer (including germ cell testicular cancer), thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer, Wilms' tumor and the like.

It is also expected that compounds having Formula (I) would inhibit growth of cells expressing Bcl-2 proteins derived from a pediatric cancer or neoplasm including embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoid/rhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitt's lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal tumors, pediatric diffuse anaplastic Wilms' tumor, pediatric favorable histology Wilms' tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric osteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer and the like.

Autoimmune disorders include acquired immunodeficiency disease syndrome (AIDS), autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, and thrombocytopenia, acute or chronic immune disease associated with organ transplantation, Addison's disease, allergic diseases, alopecia, alopecia areata, atheromatous disease/arteriosclerosis, atherosclerosis, arthritis (including osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis and reactive arthritis), autoimmune bullous disease, abetalipoproteinemia, acquired immunodeficiency-related diseases, acute immune disease associated with organ transplantation, acquired acrocyanosis, acute and chronic parasitic or infectious processes, acute pancreatitis, acute renal failure, acute rheumatic fever, acute transverse myelitis, adenocarcinomas, arial ectopic beats, adult (acute) respiratory distress syndrome, AIDS dementia complex, alcoholic cirrhosis, alcohol-induced liver injury, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allergy and asthma, allograft rejection, alpha-1-antitrypsin deficiency, Alzheimer's disease, amyotrophic lateral sclerosis, anemia, angina pectoris, ankylosing spondylitis associated lung dis-

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ease, anterior horn cell degeneration, antibody mediated cytotoxicity, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, arthropathy, asthenia, asthma, ataxia, atopic allergy, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, atrophic autoimmune hypothyroidism, autoimmune haemolytic anaemia, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), autoimmune mediated hypoglycaemia, autoimmune neutropaenia, autoimmune thrombocytopenia, autoimmune thyroid disease, B cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bronchiolitis obliterans, bundle branch block, burns, cachexia, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy associated disorders, chlamydia, cholestatitis, chronic alcoholism, chronic active hepatitis, chronic fatigue syndrome, chronic immune disease associated with organ transplantation, chronic eosinophilic pneumonia, chronic inflammatory pathologies, chronic mucocutaneous candidiasis, chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal common varied immunodeficiency (common variable hypogammaglobulinaemia), conjunctivitis, connective tissue disease associated interstitial lung disease, contact dermatitis, Coombs positive haemolytic anaemia, cor pulmonale, Creutzfeldt-Jakob disease, cryptogenic autoimmune hepatitis, cryptogenic fibrosing alveolitis, culture negative sepsis, cystic fibrosis, cytokine therapy associated disorders, Crohn's disease, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatitis scleroderma, dermatologic conditions, dermatomyositis/poly-myositis associated lung disease, diabetes, diabetic arteriosclerotic disease, diabetes mellitus, Diffuse Lewy body disease, dilated cardiomyopathy, dilated congestive cardiomyopathy, discoid lupus erythematosus, disorders of the basal ganglia, disseminated intravascular coagulation, Down's Syndrome in middle age, drug-induced interstitial lung disease, drug-induced hepatitis, drug-induced movement disorders induced by drugs which block CNS dopamine, receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, enteropathic synovitis, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hemophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, female infertility, fibrosis, fibrotic lung disease, fungal sepsis, gas gangrene, gastric ulcer, giant cell arteritis, glomerular nephritis, glomerulonephritides, Goodpasture's syndrome, goitrous autoimmune hypothyroidism (Hashimoto's disease), gouty arthritis, graft rejection of any organ or tissue, graft versus host disease, gram negative sepsis, gram positive sepsis, granulomas due to intracellular organisms, group B streptococci (GBS) infection, Grave's disease, haemosiderosis associated lung disease, hairy cell leukemia, hairy cell leukemia, Hallerorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hematopoietic malignancies (leukemia and lymphoma),

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hemolytic anemia, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, Henoch-Schoenlein purpura, Hepatitis A, Hepatitis B, Hepatitis C, HIV infection/HIV neuropathy, Hodgkin's disease, hypoparathyroidism, Huntington's chorea, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hyperthyroidism, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic leucopaenia, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia, idiosyncratic liver disease, infantile spinal muscular atrophy, infectious diseases, inflammation of the aorta, inflammatory bowel disease, insulin dependent diabetes mellitus, interstitial pneumonitis, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile pernicious anaemia, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, Kawasaki's disease, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, linear IgA disease, lipidema, liver transplant rejection, Lyme disease, lymphedema, lymphocytic infiltrative lung disease, malaria, male infertility idiopathic or NOS, malignant histiocytosis, malignant melanoma, meningitis, meningococemia, microscopic vasculitis of the kidneys, migraine headache, mitochondrial multisystem disorder, mixed connective tissue disease, mixed connective tissue disease associated lung disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel Dejerine-Thomas Shi-Drager and Machado-Joseph), myalgic encephalitis/Royal Free Disease, myasthenia gravis, microscopic vasculitis of the kidneys, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodysplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, nephrotic syndrome, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, Non-alcoholic Steatohepatitis, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, organ transplant rejection, orchitis/epididymitis, orchitis/vasectomy reversal procedures, organomegaly, osteoarthritis, osteoporosis, ovarian failure, pancreas transplant rejection, parasitic diseases, parathyroid transplant rejection, Parkinson's disease, pelvic inflammatory disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, phacogenic uveitis, *pneumocystis carinii* pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post perfusion syndrome, post pump syndrome, post-MI cardiomyopathy syndrome, postinfectious interstitial lung disease, premature ovarian failure, primary biliary cirrhosis, primary sclerosing hepatitis, primary myxoedema, primary pulmonary hypertension, primary sclerosing cholangitis, primary vasculitis, Progressive supranucleo Palsy, psoriasis, psoriasis type 1, psoriasis type 2, psoriatic arthropathy, pulmonary hypertension secondary to connective tissue disease, pulmonary manifestation of polyarteritis nodosa, post-inflammatory interstitial lung disease, radiation fibrosis, radiation therapy, Raynaud's phenomenon and disease, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, Reiter's disease, renal disease

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NOS, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, rheumatoid arthritis associated interstitial lung disease, rheumatoid spondylitis, sarcoidosis, Schmidt's syndrome, scleroderma, senile chorea, Senile Dementia of Lewy body type, sepsis syndrome, septic shock, seronegative arthropathies, shock, sickle cell anemia, Sjögren's disease associated lung disease, Sjögren's syndrome, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, sperm autoimmunity, multiple sclerosis (all subtypes), spinal ataxia, spinocerebellar degenerations, spondyloarthropathy, spondyloarthropathy, sporadic, polyglandular deficiency type I sporadic, polyglandular deficiency type II, Still's disease, streptococcal myositis, stroke, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, sympathetic ophthalmia, Syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic lupus erythematosus-associated lung disease, systemic sclerosis, systemic sclerosis-associated interstitial lung disease, T-cell or FAB ALL, Takayasu's disease/arteritis, Telangiectasia, Th2 Type and Th1 Type mediated diseases, thromboangitis obliterans, thrombocytopenia, thyroiditis, toxicity, toxic shock syndrome, transplants, trauma/hemorrhage, type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), type B insulin resistance with acanthosis nigricans, type III hypersensitivity reactions, type IV hypersensitivity, ulcerative colitic arthropathy, ulcerative colitis, unstable angina, uremia, urosepsis, urticaria, uveitis, valvular heart diseases, varicose veins, vasculitis, vasculitic diffuse lung disease, venous diseases, venous thrombosis, ventricular fibrillation, vitiligo acute liver disease, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wegener's granulomatosis, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, yersinia and salmonella-associated arthropathy and the like.

#### SCHEMES AND EXPERIMENTALS

The following abbreviations have the meanings indicated. ADDP means 1,1'-(azodicarbonyl)dipiperidine; AD-mix- $\beta$  means a mixture of (DHQD)<sub>2</sub>PHAL, K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, and K<sub>2</sub>SO<sub>4</sub>; 9-BBN means 9-borabicyclo(3.3.1)nonane; Boc means tert-butoxycarbonyl; (DHQD)<sub>2</sub>PHAL means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL means diisobutylaluminum hydride; DIEA means diisopropylethylamine; DMAP means N,N-dimethylaminopyridine; DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means dimethylsulfoxide; dppb means 1,4-bis(diphenylphosphino)-butane; dppe means 1,2-bis(diphenylphosphino)ethane; dppf means 1,1'-bis(diphenylphosphino)ferrocene; dppm means 1,1-bis(diphenylphosphino)methane; EDAC.HCl means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Fmoc means fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N',N''-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; MP-BH<sub>3</sub> means macroporous triethylammonium methylpolystyrene

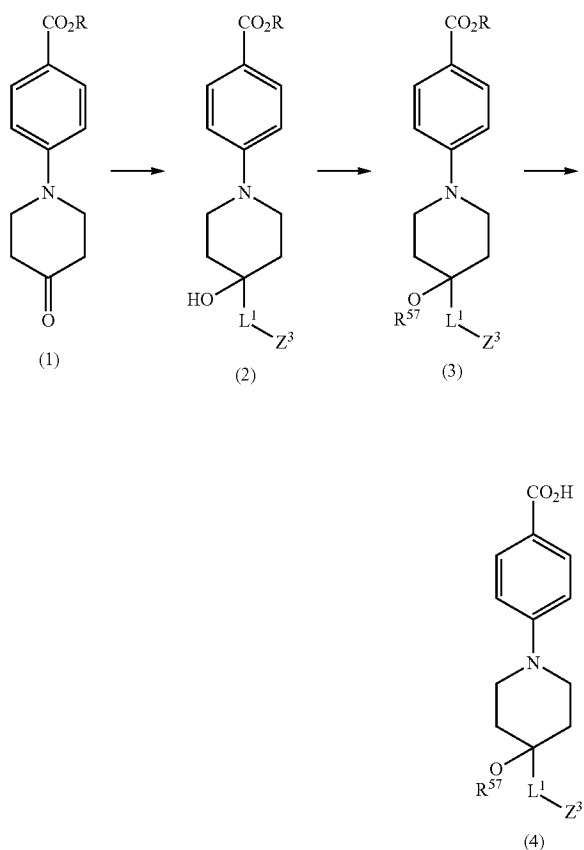
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cyanoborohydride; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP means N-methylpyrrolidine;  $\text{PPh}_3$  means triphenylphosphine.

The following schemes are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. Compounds of this invention may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

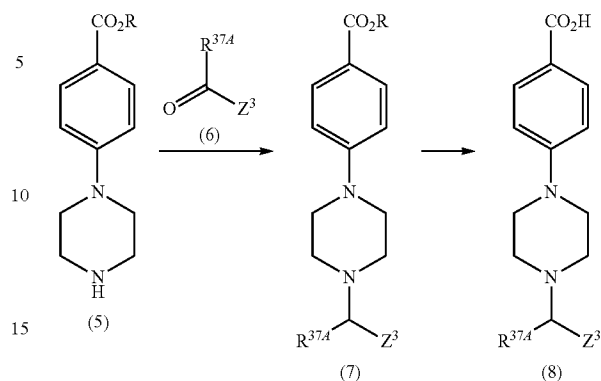
SCHEME 1



Compounds of Formula (4) can be prepared as shown in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I), which are representative of the compounds of the present invention. Compounds of Formula (I) wherein R is alkyl, can be converted to compounds of Formula (2) using  $\text{Z}^3\text{L}^1\text{MgX}^1$ , wherein  $\text{X}^1$  is a halide, in a solvent such as but not limited to ether or tetrahydrofuran. Compounds of Formula (3) can be prepared from compounds of Formula (2) using a strong base such as NaH and  $\text{R}^{37}\text{X}^2$ , wherein  $\text{X}^2$  is a halide and  $\text{R}^{37}$  is as described herein. Compounds of Formula (3), when treated with aqueous NaOH or LiOH, will provide compounds of Formula (4).

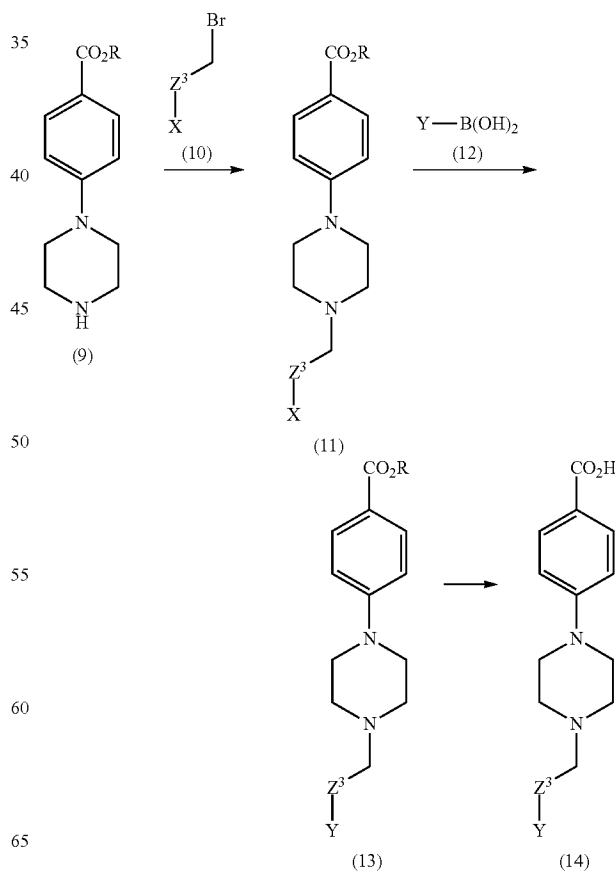
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SCHEME 2



As shown in SCHEME 2, compounds of Formula (5) can be reacted with compounds of Formula (6) and a reducing agent to provide compounds of Formula (7). Examples of reducing agents include sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, polymer supported cyanoborohydride, and the like. The reaction is typically performed in a solvent such as but not limited to methanol, tetrahydrofuran, and dichloromethane or mixtures thereof. Compounds of Formula (8) can be prepared from compounds of Formula (7) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

SCHEME 3

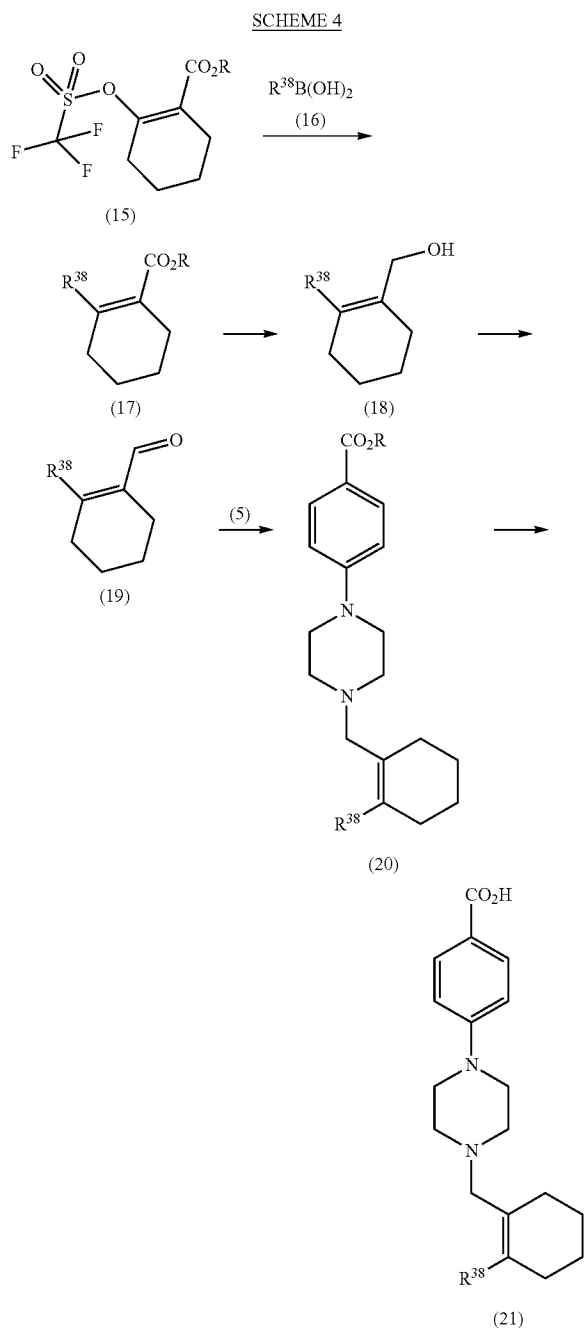




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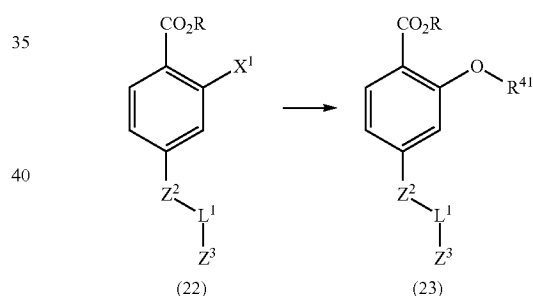
Compounds of Formula (9), when reacted with a compound of Formula (10) wherein X is a halide or triflate, and a base will provide a compound of Formula (11). Bases useful in the reaction include triethylamine, diisopropylethylamine and the like. Compounds of Formula (13), wherein Y is as described herein for substituents on Z<sup>3</sup>, can be prepared from compounds of Formula (11) and compounds of Formula (12) using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (14) can be prepared from compounds of Formula (13) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).



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As shown in SCHEME 4, compounds of Formula (17) can be prepared from compounds of Formula (15) and compounds of Formula (16), wherein R is alkyl and R<sup>38</sup> is as described herein, using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (17) can be reduced to compounds of Formula (18) using a reducing agent such as LiAlH<sub>4</sub> in a solvent such as but not limited to diethyl ether or THF. Compounds of Formula (19) can be prepared from compounds of Formula (18) using Dess-Martin periodinane or Swern oxidation conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (19) can be reacted with a compound of Formula (5) and a reducing agent to provide compounds of Formula (20). Examples of reducing agents include sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, polymer supported cyanoborohydride, and the like. The reaction is typically performed in a solvent such as but not limited to methanol, tetrahydrofuran, 1,2-dichloroethane, and dichloromethane or mixtures thereof. Compounds of Formula (21) can be prepared from compounds of Formula (20) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

## SCHEME 5



As shown in SCHEME 5, compounds of Formula (22), wherein R is alkyl, may be converted to compounds of Formula (23) by reacting the former, wherein X<sup>1</sup> is Cl, Br, I, or CF<sub>3</sub>SO<sub>3</sub>—, and compounds of Formula R<sup>41</sup>—OH and a catalyst, with or without a first base. Examples of catalysts include copper(I) trifluoromethanesulfonate toluene complex, PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, and Pd<sub>2</sub>(dba)<sub>3</sub>. Examples of first bases include triethylamine, N,N-diisopropylethylamine, Cs<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, and mixtures thereof.

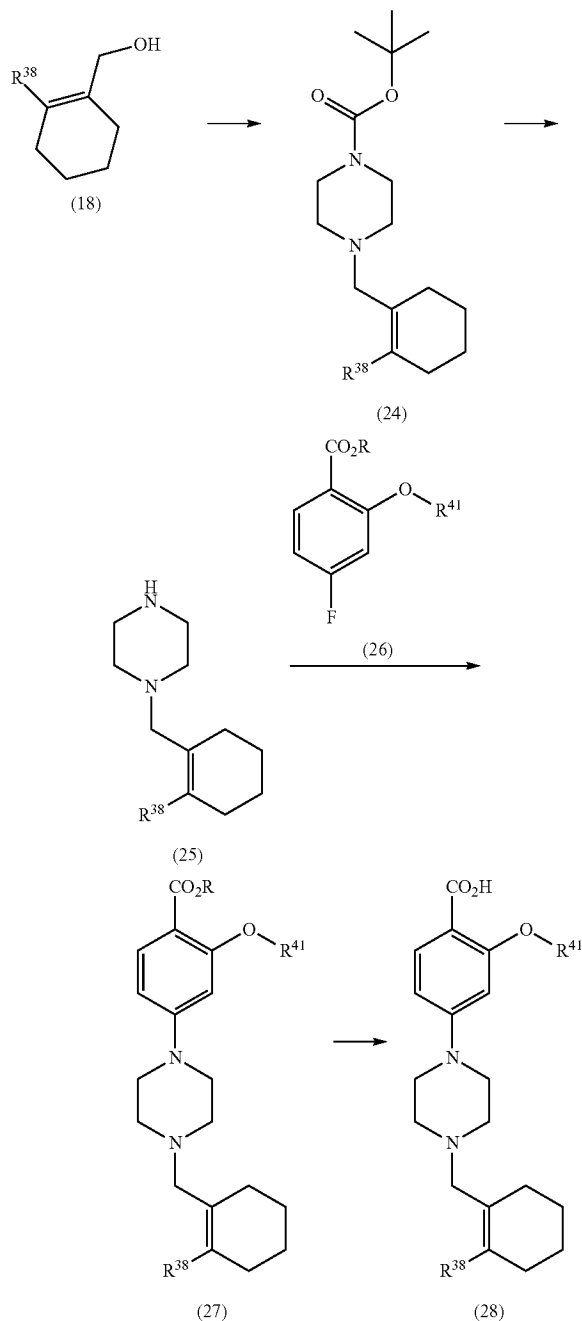
Compounds of Formula (22) may also be converted to compounds of Formula (23) by reacting the former, when X<sup>1</sup> is Cl, F, or NO<sub>2</sub>, and compounds of Formula R<sup>41</sup>—OH with a first base. Examples of first bases include triethylamine, N,N-diisopropylethylamine, Cs<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, and mixtures thereof.

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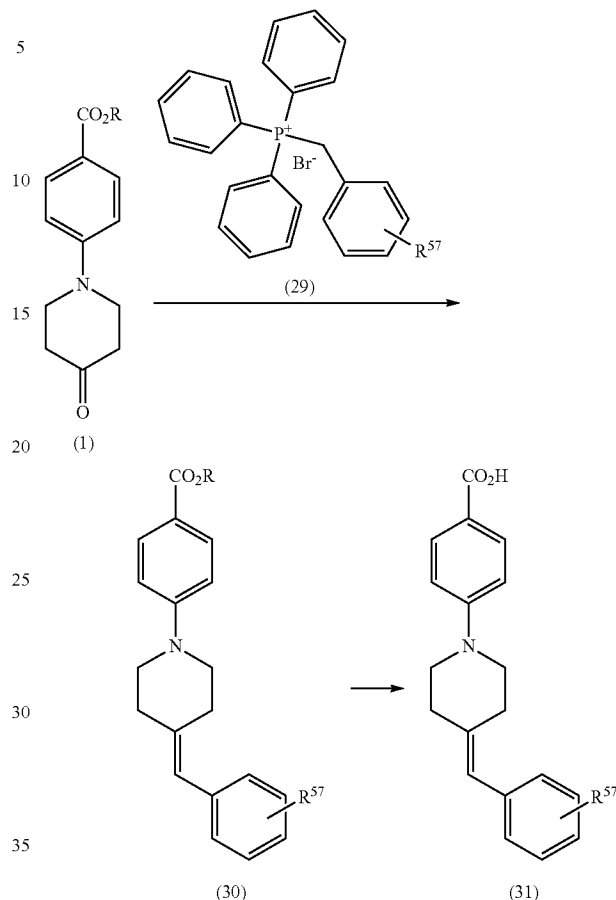
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SCHEME 6

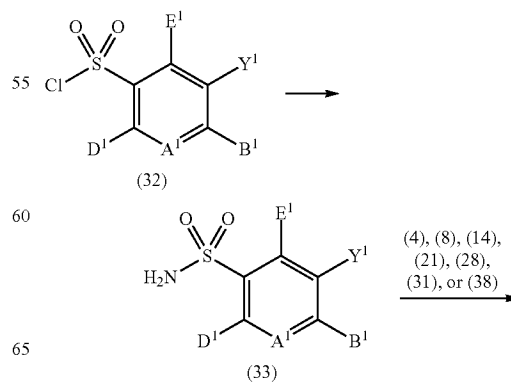


SCHEME 7



As shown in SCHEME 7, compounds of Formula (1) can be reacted with an appropriate triphenylphosphonium bromide of Formula (29) and a base such as but not limited to sodium hydride or n-butyllithium to provide compounds of Formula (30). The reaction is typically performed in a solvent such as THF or DMSO. Compounds of Formula (31) can be prepared from compounds of Formula (30) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

SCHEME 8

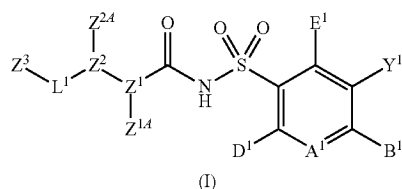


Compounds of Formula (18) can be reacted with mesyl chloride and a base such as but not limited to triethylamine, followed by N-t-butoxycarbonylpiperazine, to provide compounds of Formula (24). Compounds of Formula (25) can be prepared by reacting compounds of Formula (24) with triethylsilane and trifluoroacetic acid. Compounds of Formula (25) can be reacted with compounds of Formula (26) and HK<sub>2</sub>PO<sub>4</sub> to provide compounds of Formula (27) in a solvent such as but not limited to dimethylsulfoxide. Compounds of Formula (28) can be prepared from compounds of Formula (27) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

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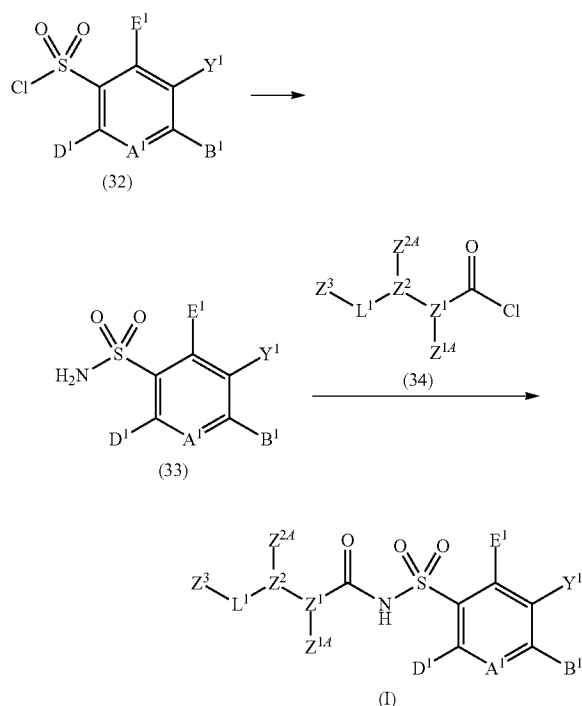
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-continued



As shown in SCHEME 8, compounds of Formula (32), which can be prepared as described herein, may be converted to compounds of Formula (33) by reacting the former with ammonia. Compounds of Formula (33) may be converted to compounds of Formula (I) by reacting the former and compounds of Formula (4), (8), (14), (21), (28), (31), or (38) and a coupling agent, with or without a first base. Examples of coupling agents include 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride, 1,1'-carbonyldiimidazole, and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate. Examples of first bases include triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, and mixtures thereof.

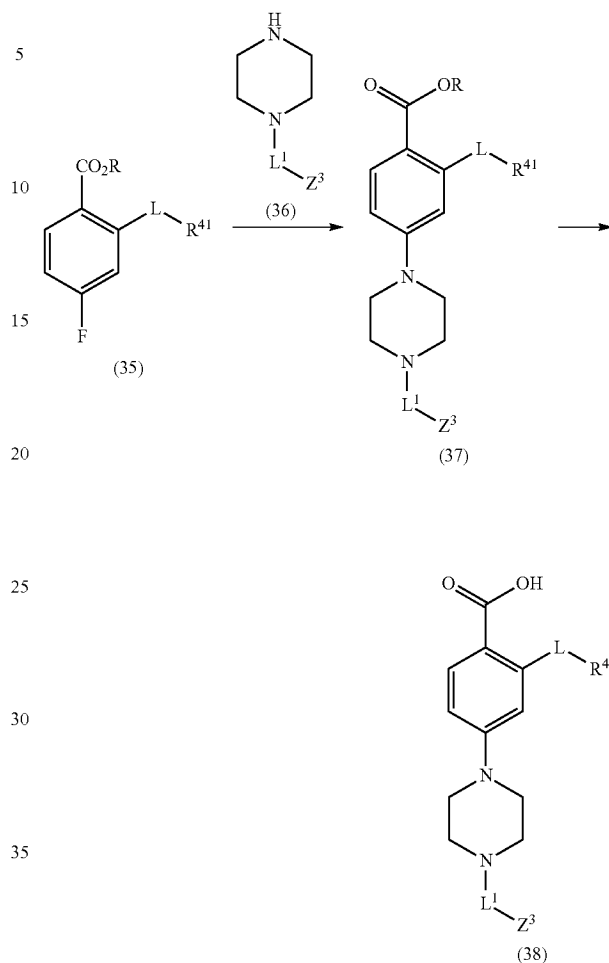
SCHEME 9



Compounds of Formula (33), prepared as described in SCHEME 8, may also be converted to compounds of Formula (I) by reacting the former and compounds of Formula (34) and a first base. Examples of first bases include but are not limited to sodium hydride, triethylamine, N,N-diisopropylethylamine, 4-(dimethylamino)pyridine, and mixtures thereof.

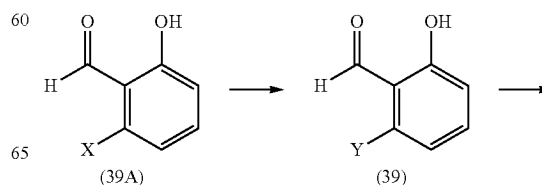
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SCHEME 10



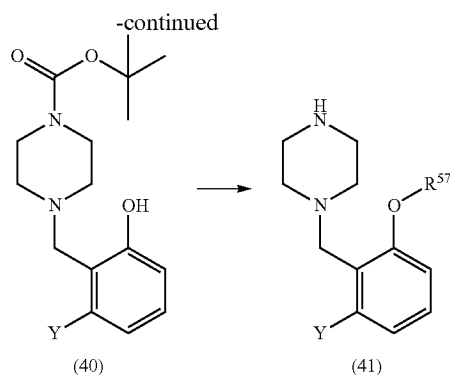
As shown in SCHEME 10, compounds of Formula (35), wherein L is a bond, alkyl, O, S, S(O), S(O)₂, NH, etc., can be reacted with compounds of Formula (36), to provide compounds of Formula (37). The reaction is typically performed at elevated temperatures in a solvent such as but not limited to dimethylsulfoxide, and may require the use of a base such as but not limited to potassium phosphate, potassium carbonate, and the like. Compounds of Formula (38) can be prepared from compounds of Formula (37) as described in SCHEME 1, and can be used as described in SCHEME 8 to prepare compounds of Formula (I).

SCHEME 11



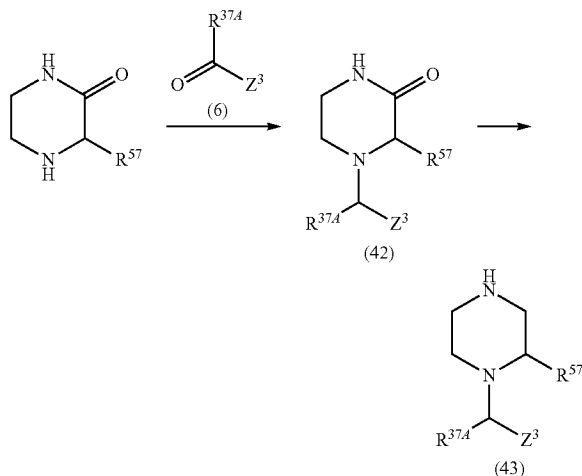
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Compounds of Formula (39), wherein Y is as described herein for substituents on Z<sup>3</sup>, can be prepared from compounds of Formula (39A) wherein X is a halide or triflate, and Y—B(OH)<sub>2</sub> using Suzuki coupling conditions known to those skilled in the art and readily available in the literature. Compounds of Formula (39) can be reacted with tert-butyl piperazine-1-carboxylate and a reducing agent such as sodium triacetoxyborohydride to provide compounds of Formula (40). The reaction is typically performed in a solvent such as but not limited to methylene chloride. Compounds of Formula (41) can be prepared from compounds of Formula (40) by reacting the latter with R<sup>57</sup>X, wherein X is a halide, and NaH in a solvent such as N,N-dimethylformamide, and then the resulting material can be treated with triethylsilane and trifluoroacetic acid in dichloromethane. Compounds of Formula (41) can be used as described in Scheme 10 wherein L<sup>1</sup>-Z<sup>3</sup> is as shown in Formula (41).

SCHEME 12



As shown in SCHEME 12, substituted piperazin-2-ones wherein R<sup>57</sup> is alkyl, can be reacted with compounds of Formula (6) and a reducing agent such as sodium triacetoxyborohydride in dichloromethane to provide compounds of Formula (42). Compounds of Formula (42) can be reduced to compounds of Formula (43) using a reducing agent such as but not limited to lithium aluminum hydride in a solvent such as but not limited to tetrahydrofuran. Compounds of Formula (43) can be used as described in Scheme 10 wherein L<sup>1</sup>-Z<sup>3</sup> is as shown in Formula (43).

The following examples are presented to provide what is believed to be the most useful and readily understood descrip-

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tion of procedures and conceptual aspects of this invention. The exemplified compounds were named using ACD/ChemSketch Version 5.06 (5 Jun. 2001, Advanced Chemistry Development Inc., Toronto, Ontario), ACD/ChemSketch Version 12.01 (13 May 2009), Advanced Chemistry Development Inc., Toronto, Ontario), or ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, Mass.). Intermediates were named using ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, Mass.).

## Example 1

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 1A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)piperazine-1-carboxylate

4'-Chlorobiphenyl-2-carboxaldehyde (4.1 g), tert-butyl piperazine-1-carboxylate (4.23 g), and sodium triacetoxyborohydride (5.61 g) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) were stirred for 24 hours. The reaction was quenched with methanol and poured into ether. The solution was washed with water and brine, concentrated, and chromatographed on silica gel with 2-25% ethyl acetate/hexanes.

## Example 1B

1-((4'-chlorobiphenyl-2-yl)methyl)piperazine

EXAMPLE 1A (3.0 g) and triethylsilane (1 mL) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and trifluoroacetic acid (30 mL) for 2 hours, and the reaction was concentrated, and then taken up in ether and concentrated again. The material was taken up in dichloromethane (200 mL) and NaHCO<sub>3</sub> solution (100 mL), and partitioned. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and condensed to give the title compound.

## Example 1C

tert-butyl 4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)-2-fluorobenzoate

Tert-butyl 4-bromo-2-fluorobenzoate (14.0 g), EXAMPLE 1B (16.05 g), Pd<sub>2</sub>(dba)<sub>3</sub> (tris(dibenzylideneacetone)dipalladium(0)) (1.40 g), 2-(di-tert-butylphosphino)biphenyl (1.82 g), and K<sub>3</sub>PO<sub>4</sub> (16.2 g) were stirred in 1,2-dimethoxyethane (300 mL) at 80° C. for 24 hours. The reaction was cooled and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 1D

tert-butyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoate

1H-Pyrrolo[2,3-B]pyridine-5-ol (167 mg), EXAMPLE 1C (500 mg), and Cs<sub>2</sub>CO<sub>3</sub> (508 mg) were stirred in dimethylsulfoxide (5 mL) at 130° C. for 24 hours. The mixture was cooled, diluted with ethyl acetate, washed three times with water, and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concen-



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trated. The crude product was chromatographed on silica gel with 25% ethyl acetate/hexanes.

**Example 1E**

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((4'-chlorobiphenyl-2-yl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 1D (200 mg) and triethylsilane (1 mL) were stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with NaH<sub>2</sub>PO<sub>4</sub>, and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated.

**Example 1F**

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(tetrahydropyran-4-yl)methylamine (1.14 g), and triethylamine (1 g) were stirred in tetrahydrofuran (30 mL) for 24 hours. The solution was diluted with ethyl acetate, washed with NaH<sub>2</sub>PO<sub>4</sub> solution and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The product was triturated from ethyl acetate.

**Example 1G**

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 1E (115 mg), EXAMPLE 1F (67 mg), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (82 mg), and 4-dimethylaminopyridine (26 mg) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) for 24 hours. The reaction was cooled and chromatographed on silica gel with 0-5% methanol/ethyl acetate. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.48 (brs, 1H), 8.34 (br s, 1H), 8.31 (m, 1H), 7.90 (d, 1H), 7.68 (m, 1H), 7.58 (m, 2H), 7.46 (m, 4H), 7.35 (m, 2H), 7.21 (dd, 1H), 6.76 (m, 4H), 6.28 (m, 2H), 3.02 (m, 2H), 2.89 (m, 4H), 2.80 (m, 4H), 2.40 (m, 3H), 1.59 (m, 2H), 1.25 (m, 4H), 0.87 (m, 2H).

**Example 2**

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 2A**

4-(3-morpholinopropylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 3-(N-morpholinyl)-propylamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 2B**

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300

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MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (brs, 1H), 8.60 (m, 1H), 8.43 (d, 1H), 7.94 (d, 1H), 7.64 (m, 2H), 7.54 (d, 1H), 7.45 (m, 4H), 7.33 (m, 2H), 7.23 (dd, 1H), 6.96 (d, 1H), 6.85 (m, 2H), 6.32 (d, 1H), 6.26 (d, 1H), 3.60 (m, 4H), 3.10 (m, 4H), 3.05 (m, 10H), 2.40 (m, 2H), 2.33 (m, 2H), 1.77 (m, 2H).

**Example 3**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 3A**

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

**Example 3B**

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 3A (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

**Example 3C**

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH<sub>4</sub> (13 g), EXAMPLE 3B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

**Example 3D**

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 3C (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and

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concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 3E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 3D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 3F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 3G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 3F (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M NaOH (69 mL) was added, followed by 30% H<sub>2</sub>O<sub>2</sub> (8.43 mL), and the solution was stirred for 1 hour. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH<sub>2</sub>PO<sub>4</sub>. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 3H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 3G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water,

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and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 3I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 3H (1.55 g), EXAMPLE 3E (2.42 g), and HK<sub>2</sub>PO<sub>4</sub> (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed with 3×1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 3J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 3I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 3K

tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

Tert-butyl piperidin-4-ylcarbamate (45.00 g, 225 mmol) and dihydro-2H-pyran-4(3H)-one (24.74 g, 247 mmol) were added to dichloromethane (1000 mL). Sodium triacetoxyborohydride (61.90 g, 292 mmol) was added, and the solution was stirred at room temperature for 16 hours. The solution was extracted with 1M sodium hydroxide and dried over anhydrous sodium sulfate. The solution was filtered and concentrated and purified by flash column chromatography on silica gel with 10% methanol (in dichloromethane) increasing to 20% methanol (in dichloromethane).

## Example 3L

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-amine dihydrochloride

A solution of EXAMPLE 3K (52.57 g, 185 mmol) in dichloromethane (900 mL) was treated with 4M aqueous HCl (462 mL), and the solution was mixed vigorously at room temperature for 16 hours. Solvent was removed under vacuum to give crude product as the dihydrochloride salt, which was used without further purification.

## Example 3M

3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)benzenesulfonamide

EXAMPLE 3L (22.12 g, 86 mmol) was added to 1,4-dioxane (300 mL) and water (43 mL). Triethylamine (43.6 mL, 31.6 g, 313 mmol) was added, and the mixture was stirred at room temperature until EXAMPLE 3L had completely dissolved. 4-chloro-3-nitrobenzenesulfonamide was

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added and the mixture was heated at 90° C. for 16 hours. The mixture was cooled, and the solvents were removed under vacuum. 10% methanol (in dichloromethane) was added and the solution was stirred vigorously at room temperature until a fine suspension was obtained. The solid was isolated by vacuum filtration and washed with dichloromethane to give pure product.

**Example 3N**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 3M for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (brs, 1H), 8.53 (br s, 1H), 8.18 (m, 1H), 8.00 (br s, 1H), 7.63 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.20 (d, 1H), 3.95 (m, 2H), 3.05 (m, 10H), 2.73 (m, 4H), 2.17 (m, 10H), 1.95 (m, 2H), 1.80 (m, 2H), 1.63 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 4**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 4A**

4-(1-methylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 4-amino-N-methylpiperidine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 4B**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (brs, 1H), 8.55 (br s, 1H), 8.17 (m, 1H), 8.02 (d, 1H), 7.85 (dd, 1H), 7.51 (m, 3H), 7.35 (m, 2H), 7.18 (dd, 1H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (d, 1H), 6.20 (d, 1H), 3.90 (m, 1H), 3.09 (m, 8H), 2.77 (m, 2H), 2.05-2.30 (m, 10H), 1.95 (s, 3H), 1.39 (t, 2H), 1.24 (m, 2H), 0.93 (s, 6H).

**Example 5**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 5A**

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(tetrahydropyran-4-yl)methylamine (1.14 g), and tri-

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ethylamine (1 g) in tetrahydrofuran (30 mL) were stirred overnight, neutralized with concentrated HCl and concentrated. The residue was suspended in ethyl acetate and the precipitates were collected, washed with water and dried to provide the title compound.

**Example 5B**

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

**Example 5C**

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 5B (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

**Example 5D**

((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH<sub>4</sub> (13 g), EXAMPLE 5C (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

**Example 5E**

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 5D (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

**Example 5F**

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 5E (200 mg) and triethylsilane (1 mL) were stirred in dichloromethane (15 mL) and trifluoroacetic acid

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(15 mL) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with  $\text{NaH}_2\text{PO}_4$ , and brine, and dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated.

## Example 5G

## 5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 5H

## 1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 5G (24.3 g) in tetrahydrofuran (500 mL) at  $-78^\circ\text{C}$ . as added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at  $0^\circ\text{C}$ ., and 1M NaOH (69 mL) was added, followed by 30%  $\text{H}_2\text{O}_2$  (8.43 mL), and the solution was stirred for 1 hour.  $\text{Na}_2\text{S}_2\text{O}_3$  (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid  $\text{NaH}_2\text{PO}_4$ . The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 5I

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 5H (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and  $\text{K}_3\text{PO}_4$  (9.32 g) in diglyme (40 mL) at  $115^\circ\text{C}$ . was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 5J

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 5I (1.55 g), EXAMPLE 5F (2.42 g), and  $\text{HK}_2\text{PO}_4$  (1.42 g) in dimethylsulfoxide (20 mL) at  $135^\circ\text{C}$ . was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed with 3x1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

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## Example 5K

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 5J (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at  $50^\circ\text{C}$ . was stirred for 24 hours. The reaction was cooled, added to  $\text{NaH}_2\text{PO}_4$  solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 5L

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 5K (3.39 g), EXAMPLE 5A (1.87 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (2.39 g), and 4-dimethylaminopyridine (1.09 g) were stirred in  $\text{CH}_2\text{Cl}_2$  (40 mL) for 24 hours. The reaction was cooled and chromatographed on silica gel with 25-100% ethyl acetate/hexanes, then 10% methanol/ethyl acetate with 1% acetic acid, to give the product (1.62 g, 32%) as a white solid.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ ) 11.65 (br s, 1H), 8.55 (br s, 1H), 8.04 (d, 1H), 7.89 (dd, 1H), 7.51 (m, 3H), 7.33 (d, 2H), 7.08 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.84 (m, 1H), 3.30 (m, 4H), 3.07 (m, 4H), 2.73 (m, 2H), 2.18 (m, 6H), 1.95 (m, 2H), 1.61 (dd, 2H), 1.38 (m, 2H), 1.24 (m, 4H), 0.92 (s, 6H).

## Example 6

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 6A

## 4-(4-methylpiperazin-1-ylamino)-3-nitrobenzenesulfonamide

A 50 mL round-bottomed flask was charged with 4-chloro-3-nitrobenzenesulfonamide (1 g, 4.23 mmol), 4-methylpiperazin-1-amine dihydrochloride (1 g, 5.32 mmol), and  $\text{N}^1, \text{N}^1, \text{N}^2, \text{N}^2$ -tetramethylethane-1,2-diamine (3 mL, 20.01 mmol) in dioxane (10 mL). The reaction mixture was refluxed for 12 hours. After this time, the reaction mixture was cooled to room temperature, the salt filtered off via a Buchner funnel, and the solvent removed in vacuo. The crude product was added to a silica gel column (Analogix, SF65-200g) and purified by eluting with 0-5% methanol in dichloromethane.

## Example 6B

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 6A for EXAMPLE 1F in EXAMPLE 1G.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide-



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$d_6$ )  $\delta$  11.65 (brs, 1H), 9.09 (br s, 1H), 8.47 (d, 1H), 8.24 (dd, 1H), 7.99 (d, 1H), 7.50 (m, 4H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.35 (d, 1H), 6.20 (d, 1H), 3.04 (m, 4H), 2.89 (m, 4H), 2.73 (m, 2H), 2.34 (s, 3H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.38 (t, 2H), 1.05 (m, 4H), 0.93 (s, 6H).

## Example 7

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(3-nitrophenyl)sulfonylbenzamide

## Example 7A

ethyl 2-(9H-carbazol-4-yloxy)-4-fluorobenzoate

This EXAMPLE was prepared by substituting ethyl 2,4-difluorobenzoate for methyl 2,4-difluorobenzoate and 4-hydroxycarbazole for EXAMPLE 3G in EXAMPLE 3H.

## Example 7B

ethyl 2-(9H-carbazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate

This EXAMPLE was prepared by substituting EXAMPLE 7A for EXAMPLE 3H in EXAMPLE 3I.

## Example 7C

2-(9H-carbazol-4-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

This EXAMPLE was prepared by substituting EXAMPLE 7B for EXAMPLE 3I in EXAMPLE 3J, except here upon completion of the reaction, water and 2N HCl were added to adjust the pH to 2, and the HCl salt of the product was extracted using  $\text{CHCl}_3/\text{CH}_3\text{OH}$ .

## Example 7D

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(3-nitrophenyl)sulfonylbenzamide

This EXAMPLE was prepared by substituting EXAMPLE 7C for EXAMPLE 1E and EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G, except here the purification was done by preparative HPLC using a C18 column, 250x50 mm, 10 $\mu$ , and eluting with a gradient of 20-100%  $\text{CH}_3\text{CN}$  vs. 0.1% trifluoroacetic acid in water, giving the product as a bistrifluoroacetate salt.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.82 (br s, 1H), 11.40 (s, 1H), 9.70, 9.40 (both v br s, total 2H), 8.40 (d, 1H), 8.10 (br d, 1H), 7.90 (br d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.48 (d, 1H), 7.38 (m, 3H), 7.22 (m, 2H), 7.07 (m, 4H), 6.78 (dd, 1H), 6.43 (dd, 1H), 6.19 (s, 1H), 3.97 (m, 1H), 3.80 (m, 2H), 3.60, 3.30, 3.10, 2.80 (all br m, total 11H), 2.20, 2.10, 2.00 (all br m, total 8H), 1.78 (m, 2H), 1.42 (m, 2H), 1.25 (m, 2H), 0.92 (s, 6H).

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## Example 8

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl)sulfonylbenzamide

## Example 8A

3-nitro-4-(3-(pyrrolidin-1-yl)propylamino)benzenesulfonamide

This EXAMPLE was prepared by substituting 3-(pyrrolidin-1-yl)propan-1-amine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 8B

2-(9H-carbazol-4-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(3-nitro-4-[(3-pyrrolidin-1-ylpropyl)amino]phenyl)sulfonylbenzamide

This EXAMPLE was prepared by substituting EXAMPLE 7C for EXAMPLE 1E and EXAMPLE 8A for EXAMPLE 1F in EXAMPLE 1G, except here the purification was done by preparative HPLC using a C18 column, 250x50 mm, 10 $\mu$ , and eluting with a gradient of 20-100%  $\text{CH}_3\text{CN}$  vs. 0.1% trifluoroacetic acid in water, giving the product as a bistrifluoroacetate salt.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.80 (brs, 1H), 11.42 (s, 1H), 9.50, 9.25 (both v br s, total 2H), 8.58 (br t, 1H), 8.43 (d, 1H), 7.91 (d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.38 (m, 3H), 7.23 (m, 2H), 7.07 (m, 3H), 6.93 (d, 1H), 6.78 (dd, 1H), 6.44 (dd, 1H), 6.18 (s, 1H), 3.70, 3.60, 3.20, 3.00 (all br m, total 18H), 2.18 (br m, 2H), 2.00-1.80 (envelope, 8H), 1.42 (m, 2H), 0.92 (s, 6H).

## Example 9

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 9A

Trans-tert-butyl 4-morpholinocyclohexylcarbamate

A solution of tert-butyl 4-aminocyclohexylcarbamate (20.32 g, 95 mmol), bis(2-bromoethyl)ether (14.30 ml, 114 mmol) and triethylamine (33.0 ml, 237 mmol) in N,N-dimethylformamide (200 ml) was stirred for 16 hours at 70° C. The reaction mixture was cooled down to room temperature, concentrated and the product was extracted with ethyl acetate. The organic layer was washed with sodium carbonate solution (15% aq.), dried and concentrated. The product was used in next step without purification.

## Example 9B

Trans-4-morpholinocyclohexanamine dihydrochloride

To a solution of trans-tert-butyl 4-morpholinocyclohexylcarbamate (19.2 g, 67.5 mmol) in dichloromethane (100 ml) was added HCl (100 ml, 400 mmol) (4M in dioxane) and the

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reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was diluted with ether and solid salt was filtered off, and dried in an oven.

**Example 9C**

Trans-4-(4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

A solution of trans-4-morpholinocyclohexylamine dihydrochloride (5 g, 19.44 mmol), 4-fluoro-3-nitrobenzenesulfonamide (4.32 g, 19.63 mmol) and triethylamine (20 ml, 143 mmol) in tetrahydrofuran (60 ml) was stirred for 16 hours at room temperature. The solid product was filtered off, washed with tetrahydrofuran, ether, dichloromethane (3×) and dried under vacuum.

**Example 9D**

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-morpholin-4-ylcyclohexylamino)-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 9C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (brs, 1H), 8.49 (br s, 1H), 8.12 (m, 1H), 7.99 (br s, 1H), 7.71 (m, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 7.01 (m, 1H), 6.65 (dd, 1H), 6.36 (d, 1H), 6.21 (d, 1H), 3.60 (m, 4H), 3.04 (m, 4H), 2.73 (m, 2H), 2.57 (m, 2H), 2.42 (m, 1H), 2.18 (m, 6H), 2.05 (m, 2H), 1.95 (m, 2H), 1.90 (m, 2H), 1.38 (m, 6H), 1.15 (m, 3H), 0.92 (s, 6H).

**Example 10**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{[2-methoxyethyl]amino}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 10A**

4-(2-methoxyethylamino)-3-nitrobenzenesulfonamide

This EXAMPLE was prepared by substituting 2-methoxyethylamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 10B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(4-{[2-methoxyethyl]amino}-3-nitrophenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 10A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (brs, 1H), 8.58-8.49 (m, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.79 (m, 1H), 7.49 (m, 3H), 7.34 (m, 2H), 7.06 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.61-3.51 (m, 4H), 3.31 (s, 3H), 3.07 (m, 4H), 2.74 (m, 2H), 2.17 (m, 6H), 1.95 (br s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 11A**

(S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide and (R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

This EXAMPLE was prepared by substituting (tetrahydro-2H-pyran-3-yl)methanamine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 11B**

(S)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

The racemic mixture of EXAMPLE 11A was resolved by chiral SFC on an AD column (21 mm i.d.×250 mm in length) using a gradient of 10-30% 0.1% diethylamine methanol in CO<sub>2</sub> over 15 minutes (oven temperature: 40° C.; flow rate: 40 mL/minute) to provide the title compound.

**Example 11C**

(R)-3-nitro-4-((tetrahydro-2H-pyran-3-yl)methylamino)benzenesulfonamide

The racemic mixture of EXAMPLE 11A was resolved by chiral SFC on an AD column (21 mm i.d.×250 mm in length) using a gradient of 10-30% 0.1% diethylamine methanol in CO<sub>2</sub> over 15 minutes (oven temperature: 40° C.; flow rate: 40 mL/minute) to provide the title compound.

**Example 11D**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a mixture of EXAMPLE 3J (59.8 mg, 0.105 mmol), EXAMPLE 11B (33 mg, 0.105 mmol) and N,N-dimethylpyridin-4-amine (38.4 mg, 0.314 mmol) in dichloromethane (5 ml) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (24.07 mg, 0.13 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 ml) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.40 (s, br, 1H), 8.53-8.58 (m, 2H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47-7.54 (m, 3H), 7.34 (d, 2H), 7.02-7.09 (m, 3H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.79 (dd, 1H), 3.69-3.73 (m, 1H), 3.22-3.37 (m, 3H), 3.16-3.21 (m, 1H), 3.07 (s, 4H),

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2.74 (s, 2H), 2.09-2.24 (m, 6H), 1.95 (s, 2H), 1.86-1.93 (m, 1H), 1.79-1.85 (m, 1H), 1.58-1.64 (m, 1H), 1.42-1.51 (m, 1H), 1.38 (t, 2H), 1.25-1.34 (m, 1H), 0.92 (s, 6H).

## Example 12

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 12A

4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzene-sulfonamide

(1,4-Dioxan-2-yl)methanol (380 mg, 3.22 mmol) in tetrahydrofuran (30 mL) was treated with sodium hydride (60%) (245 mg, 6.13 mmol) at room temperature for 30 minutes. The reaction mixture was cooled in an ice bath and 4-fluoro-3-nitrobenzenesulfonamide (675 mg, 3.06 mmol) was added. The resulting mixture was stirred at room temperature for 2 hours and another portion of sodium hydride (60%) (245 mg, 6.13 mmol) was added. The reaction mixture was stirred overnight and quenched with ice water (3 mL). The cloudy mixture was filtered and the filtrate was concentrated. The residue was triturated with methanol to give the title compound.

## Example 12B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 12A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.42 (s, br, 1H), 8.34 (s, 1H), 8.03 (d, 2H), 7.48-7.55 (m, 3H), 7.41 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.20-4.28 (m, 2H), 3.85-3.91 (m, 1H), 3.82 (dd, 1H), 3.74-3.78 (m, 1H), 3.59-3.69 (m, 2H), 3.41-3.51 (m, 2H), 3.05-3.17 (m, 4H), 2.83 (s, br, 2H), 2.27 (s, br, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 13

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 11C in place of EXAMPLE 11B. The proton NMR spectra of EXAMPLE 13 and EXAMPLE 11D are identical. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.40 (s, br, 1H), 8.53-8.58 (m, 2H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47-7.54 (m, 3H), 7.34 (d, 2H), 7.02-7.09 (m, 3H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.79 (dd, 1H), 3.69-3.73 (m, 1H), 3.22-3.37 (m, 3H), 3.16-3.21 (m, 1H), 3.07 (s, 4H), 2.74 (s, 2H), 2.09-2.24 (m, 6H), 1.95 (s, 2H), 1.86-1.93 (m, 1H), 1.79-1.85 (m, 1H), 1.58-1.64 (m, 1H), 1.42-1.51 (m, 1H), 1.38 (t, 2H), 1.25-1.34 (m, 1H), 0.92 (s, 6H).

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## Example 14

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(2-naphthylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using naphthalene-2-sulfonamide (47 mg, 0.227 mmol) in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.82 (s, 1H), 11.69 (s, 1H), 8.51 (s, 1H), 8.08 (d, 1H), 8.05 (d, 1H), 7.97 (dd, 2H), 7.82 (dd, 1H), 7.66-7.71 (m, 1H), 7.63 (t, 1H), 7.54 (d, 1H), 7.47-7.52 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.65 (dd, 1H), 6.39 (dd, 1H), 6.18 (s, 1H), 3.04 (s, 4H), 2.72 (s, 2H), 2.10-2.20 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 15

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 15A

methyl 6,6-dimethyl-4-oxotetrahydro-2H-pyran-3-carboxylate

To a suspension of hexane-washed NaH (0.72 g, 60% in mineral oil) in tetrahydrofuran (30 mL) was added a solution of 2,2-dimethyldihydro-2H-pyran-4(3H)-one (2.0 g) in tetrahydrofuran (20 mL). The suspension was stirred at room temperature for 30 minutes. The dimethylcarbonate (6.31 mL) was added dropwise by syringe. The mixture was heated to reflux for 4 h. LC/MS showed the expected product as the major product. The mixture was acidified with 5% HCl and extracted with dichloromethane (100 mL×3) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation, the crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

## Example 15B

methyl 6,6-dimethyl-4-(trifluoromethylsulfonyloxy)-5,6-dihydro-2H-pyran-3-carboxylate

To a cooled (0° C.) stirring suspension of NaH (0.983 g, 60% in mineral oil) in ether (50 mL) was added EXAMPLE 15A (3.2 g). The mixture was stirred at 0° C. for 30 minutes before the addition of Tf<sub>2</sub>O (4.2 mL). The mixture was then stirred at room temperature overnight. The mixture was diluted with ether (200 mL) and washed with 5% HCl, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, evaporation of solvent gave the crude product which was used in the next step without further purification.

## Example 15C

methyl 4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carboxylate

To a solution of EXAMPLE 15B (2.88 g), 4-chlorophenylboronic acid (1.88 g) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.578 g) in toluene (40 mL) and ethanol (10 mL) was added 2N Na<sub>2</sub>CO<sub>3</sub> (10 mL). The mixture was stirred at reflux overnight. The mixture was diluted ether (300 mL) and washed with water, brine and

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dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent, the residue was loaded on a column and eluted with 3% ethyl acetate in hexane to give the product.

## Example 15D

(4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methanol

To a solution of EXAMPLE 15C (1.6 g) in ether (20 mL) was added LiAlH<sub>4</sub> (1.2 g). The mixture was stirred for 4 hours. The mixture was acidified carefully with 5% HCl and extracted with ethyl acetate (100 mL×3) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After concentration, the crude product was loaded on a column and eluted with 10% ethyl acetate in hexane to give the product.

## Example 15E

4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-carbaldehyde

To a solution of oxalyl chloride (1.1 g) in dichloromethane (30 mL) at -78° C. was added dimethylsulfoxide (6.12 mL). The mixture was stirred at the temperature for 30 minutes, and then a solution of EXAMPLE 15D (1.2 g) in dichloromethane (10 mL) was added. The mixture was stirred at -78° C. for 2 hours before the addition of triethylamine (10 mL). The mixture was stirred overnight and the temperature was allowed to rise to room temperature. The mixture was diluted with ether (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration of the solvent and column purification (5% ethyl acetate in hexane) gave the product.

## Example 15F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(piperazin-1-yl)benzoate

A mixture of EXAMPLE 3H (20.5 g) and piperazine (37.0 g) in dimethylsulfoxide (200 mL) was heated to 110° C. for 24 hours, and the mixture was allowed to cool to room temperature. The mixture was poured into water (1 L), extracted three times with dichloromethane, and the combined extracts were washed with 2× water, and brine and filtered and concentrated to give the pure product.

## Example 15G

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 15E (100 mg) and EXAMPLE 15F (177 mg) in dichloromethane (10 mL) was added sodium triacetoxyborohydride (154 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2% NaOH, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum. The residue was loaded on a column and eluted with 30% ethyl acetate in hexane to give the pure product.

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## Example 15H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoic acid

To a solution of EXAMPLE 15G (254 mg) in tetrahydrofuran (4 mL), methanol (2 mL) and water (2 mL) was added LiOH H<sub>2</sub>O (126 mg). The mixture was stirred overnight. The mixture was then neutralized with 5% HCl and diluted with ethyl acetate (200 mL). After washing with brine, it was dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of solvent gave the product.

## Example 15I

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G, substituting EXAMPLE 1E with EXAMPLE 15H. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (br s, 1H), 11.42 (s, 1H), 8.60 (m, 1H), 8.57 (d, 1H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.48-7.54 (m, 3H), 7.38 (d, 2H), 7.12 (m, 3H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.11 (s, 2H), 3.85 (m, 2H), 3.27 (m, 6H), 3.07 (m, 2H), 2.84 (m, 2H), 2.14 (m, 5H), 1.92 (m, 1H), 1.42 (m, 2H), 1.24 (m, 2H), 1.10 (s, 6H).

## Example 16

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 16A

4-(2-methoxyethylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

4-Fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (1.536 g, 5 mmol), 2-methoxyethanamine (0.376 g, 5 mmol), and triethylamine (1.939 g, 15 mmol) in anhydrous tetrahydrofuran (30 mL) solution was heated at 55° C. for 3 hours. The solution was diluted with ethyl acetate, washed with water and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the filtrate was concentrated. The crude material was used in the next step without further purification.

## Example 16B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 16A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (brs, 1H), 8.14 (m, 1H), 8.03 (d, 1H), 7.91 (d, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.19 (s, 1H), 7.04 (m, 3H),



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6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.06 (m, 4H), 2.75 (m, 2H), 2.17 (m, 6H), 1.95 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 17

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]-pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

## Example 17A

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

This EXAMPLE was prepared by substituting 1-(tetrahydropyran-4-yl)methylamine for 2-methoxyethanamine in EXAMPLE 16A.

## Example 17B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

This EXAMPLE was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 17A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (brs, 1H), 8.15 (m, 1H), 8.04 (d, 1H), 7.92 (d, 1H), 7.51 (m, 3H), 7.34 (d, 2H), 7.19 (s, 1H), 7.05 (m, 3H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.18 (d, 1H), 3.85 (m, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.77 (m, 2H), 2.17 (m, 6H), 1.95 (m, 2H), 1.84 (m, 1H), 1.54 (m, 2H), 1.39 (t, 2H), 1.24 (m, 2H), 0.93 (s, 6H).

## Example 18

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

## Example 18A

methyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

A mixture of 5-hydroxyindole (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 18B

methyl 2-(1H-indol-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 18A (1.7 g), EXAMPLE 3E (1.8 g), and HK<sub>2</sub>PO<sub>4</sub> (1.21 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed with 3×1M NaOH,

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and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 18C

2-(1H-indol-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 18B (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 18D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 3J with EXAMPLE 18C, and EXAMPLE 1F for EXAMPLE 11B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.18 (s, 2H), 8.59-8.64 (m, 2H), 7.80 (dd, 1H), 7.52 (d, 1H), 7.39-7.42 (m, 2H), 7.33 (d, 2H), 7.16 (d, 1H), 7.10 (d, 1H), 7.03 (d, 2H), 6.8 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.14 (d, 1H), 3.85 (dd, 2H), 3.24-3.32 (m, 4H), 3.03 (s, 3H), 2.73 (s, 2H), 2.12-2.17 (m, 5H), 1.68-1.94 (m, 3H), 1.61 (d, 2H), 1.37 (t, 2H), 1.24-1.27 (m, 2H), 0.92 (s, 6H).

## Example 19

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-morpholin-4-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 11B with EXAMPLE 9B and EXAMPLE 3J with EXAMPLE 18C. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.29 (s, 1H), 9.29 (d, J=2.1 Hz, 1H), 8.37 (d, J=7.6 Hz, 1H), 8.32 (dd, J=9.3, 2.3 Hz, 1H), 8.18 (d, J=8.8 Hz, 1H), 7.52-7.57 (m, 2H), 7.39-7.47 (m, 3H), 7.10 (dd, J=8.7, 2.3 Hz, 1H), 7.05-7.08 (m, 2H), 6.90 (d, J=9.5 Hz, 1H), 6.74 (dd, J=9.0, 2.3 Hz, 1H), 6.59-6.63 (m, 1H), 6.55 (d, J=2.4 Hz, 1H), 3.72-3.78 (m, 4H), 3.33-3.43 (m, 1H), 2.99-3.09 (m, 4H), 2.76 (s, 2H), 2.46-2.54 (m, 4H), 2.16-2.29 (m, 3H), 2.09-2.14 (m, 4H), 2.05 (d, J=11.9 Hz, 2H), 1.97 (d, J=1.8 Hz, 2H), 1.87 (d, J=11.6 Hz, 2H), 1.19-1.42 (m, 6H), 0.93 (s, 6H).

## Example 20

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 11B with EXAMPLE 10A and EXAMPLE 3J with EXAMPLE 18C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.20 (br. s, 1H) 11.15 (s, 1H) 8.59 (m, 2H) 7.81 (dd, 1H) 7.50 (d, 1H) 7.36 (m,

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4H) 7.08 (m, 4H) 6.85 (dd, 1H) 6.65 (dd, 1H) 6.38 (m, 1H)  
6.14 (m, 1H) 3.58 (m, 4H) 3.30 (s, 3H) 3.03 (m, 4H) 2.73 (s,  
2H) 2.15 (m, 6H) 1.96 (s, 2H) 1.38 (t, 2H) 0.92 (s, 6H)

## Example 21

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3S)-tetrahydro-2H-pyran-3-ylmethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 3J with EXAMPLE 18C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.17 (s, 2H), 8.53-8.65 (m, 2H), 7.80 (d, 1H), 7.51 (d, 1H), 7.38-7.44 (m, 2H), 7.33 (d, 2H), 7.15 (s, 1H), 7.02-7.09 (m, 3H), 6.82-6.92 (m, 1H), 6.65 (d, 1H), 6.39 (s, 1H), 6.14 (s, 1H), 3.68-3.82 (m, 2H), 3.22-3.32 (m, 2H), 3.13-3.22 (m, 1H), 3.03 (s, 4H), 2.72 (s, 2H), 2.09-2.23 (m, 6H), 1.78-1.98 (m, 4H), 1.56-1.66 (m, 1H), 1.43-1.51 (m, 1H), 1.37 (t, 2H), 1.22-1.33 (m, 1H), 0.92 (s, 6H).

## Example 22

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-[(3-nitro-4-{[(3R)-tetrahydro-2H-pyran-4-ylmethyl]amino}phenyl)sulfonyl]benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 11C in place of EXAMPLE 11B, and EXAMPLE 18C in place of EXAMPLE 3J. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.17 (s, 2H), 8.53-8.65 (m, 2H), 7.80 (d, 1H), 7.51 (d, 1H), 7.38-7.44 (m, 2H), 7.33 (d, 2H), 7.15 (s, 1H), 7.02-7.09 (m, 3H), 6.82-6.92 (m, 1H), 6.65 (d, 1H), 6.39 (s, 1H), 6.14 (s, 1H), 3.68-3.82 (m, 2H), 3.22-3.32 (m, 2H), 3.13-3.22 (m, 1H), 3.03 (s, 4H), 2.72 (s, 2H), 2.09-2.23 (m, 6H), 1.78-1.98 (m, 4H), 1.56-1.66 (m, 1H), 1.43-1.51 (m, 1H), 1.37 (t, 2H), 1.22-1.33 (m, 1H), 0.92 (s, 6H).

## Example 23

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

## Example 23A

methyl 2-(1H-indol-5-yloxy)-4-(piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 15F by replacing EXAMPLE 3H with EXAMPLE 18A.

## Example 23B

methyl 2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared as described in EXAMPLE 15G by replacing EXAMPLE 15F with EXAMPLE 23A.

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## Example 23C

2-(1H-indol-5-yloxy)-4-(4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 15H by replacing EXAMPLE 15G with EXAMPLE 23B.

## Example 23D

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D by replacing EXAMPLE 11B with EXAMPLE 1F, and EXAMPLE 3J with EXAMPLE 23C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.20 (br s, 1H), 11.17 (s, 1H), 8.63 (t, 1H), 8.59 (d, 1H), 7.79 (dd, 1H), 7.51 (d, 1H), 7.36 (m, 3H), 7.13 (m, 2H), 6.86 (dd, 1H), 6.66 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.10 (s, 2H), 3.85 (m, 3H), 3.50 (m, 2H), 3.42 (m, 2H), 3.24 (m, 4H), 3.02 (m, 4H), 2.82 (m, 2H), 2.16 (m, 2H), 1.61 (m, 3H), 1.25 (m, 4H), 1.17 (s, 6H).

## Example 24

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 24A

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

(Tetrahydro-2H-pyran-4-yl)methanol (2.0 g) in tetrahydrofuran (20 mL) was treated with 60% NaH (1.377 g). The solution was stirred for 20 minutes at the room temperature. To this solution was added 4-fluoro-3-nitrobenzenesulfonamide (2.84 g) portion-wise. The reaction was stirred for another 2 hours. The mixture was poured into water, neutralized with 10% HCl, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20-60% ethyl acetate in hexanes.

## Example 24B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 24A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.33 (s, 1H), 8.00-8.02 (m, 2H), 7.50-7.53 (m, 3H), 7.34-7.36 (m, 3H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (d, 1H), 6.21 (s, 1H), 4.06 (d, 2H), 3.88 (dd, 2H), 3.08 (s, 4H), 2.80 (s, 2H), 2.25 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.66 (m, 2H), 1.52-1.55 (m, 1H), 1.33-1.40 (m, 4H), 0.92 (s, 6H).

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## Example 25

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 25A

4-((1,4-dioxan-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 1F using (1,4-dioxan-2-yl)methanamine in place of (tetrahydropyran-4-yl)methanamine.

## Example 25B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 25A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.38 (s, 1H), 8.53-8.59 (m, 2H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.46-7.54 (m, 3H), 7.34 (d, 2H), 7.09 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.75-3.86 (m, 3H), 3.58-3.68 (m, 2H), 3.45-3.52 (m, 2H), 3.35-3.43 (m, 2H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H)

## Example 26

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 26A

3-nitro-4-(2,2,2-trifluoroethylamino)benzenesulfonamide

The title compound was prepared by substituting 2,2,2-trifluoroethanamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 26B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2,2,2-trifluoroethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 26A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.48 (s, 1H), 8.40 (m, 2H), 7.90 (d, 1H), 7.71 (dd, 1H), 7.59 (d, 1H), 7.40 (t, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.06 (m, 3H), 6.61 (dd, 1H), 6.26

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(m, 2H), 4.32 (m, 2H), 3.00 (m, 4H), 2.73 (s, 2H), 2.19 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 27

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 27A

3-nitro-4-(3,3,3-trifluoropropylamino)benzenesulfonamide

The title compound was prepared by substituting 3,3,3-trifluoropropan-1-amine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 27B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(3,3,3-trifluoropropyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 27A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.47 (s, 1H), 8.37 (d, 1H), 8.29 (m, 1H), 7.89 (d, 1H), 7.61 (m, 2H), 7.39 (t, 1H), 7.35 (d, 2H), 7.22 (d, 1H), 7.05 (d, 2H), 6.75 (d, 1H), 6.62 (dd, 1H), 6.27 (m, 2H), 3.59 (q, 2H), 3.00 (m, 4H), 2.73 (s, 2H), 2.66 (m, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (m, 6H).

## Example 28

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 28A

(S)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

The racemic mixture of EXAMPLE 12A was resolved on a SFC chiral AD column to provide the title compound.

## Example 28B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2S)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 28A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 2H), 8.35 (s, 1H), 8.03 (d, 2H), 7.48-7.57 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (s, 1H), 4.19-4.30 (m, 2H), 3.85-3.92 (m, 1H), 3.73-3.85 (m, 2H), 3.58-3.70 (m, 2H), 3.40-3.52 (m, 2H), 3.10 (s, 4H), 2.85 (s, 2H), 2.18-2.39 (m, 3H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 29

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 29A

Cis-4-((4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (1.098 g) and EXAMPLE 34A (1 g) in tetrahydrofuran (20 mL) was treated with N,N-diisopropylethylamine (0.871 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography, eluted with 40-55% acetonitrile in 0.1% trifluoroacetic acid in water over 25 min to give the cis isomer EXAMPLE 29A and trans isomer EXAMPLE 34B.

## Example 29B

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 29A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.36 (s, 1H), 8.53-8.63 (m, 2H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47-7.56 (m, 3H), 7.34 (d, 2H), 7.00-7.12 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.37 (s, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.81 (dd, 2H), 1.64-1.74 (m, 1H), 1.48 (dd, 2H), 1.23-1.42 (m, 6H), 0.92 (s, 6H).

## Example 30

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 30A

(R)-4-((1,4-dioxan-2-yl)methoxy)-3-nitrobenzenesulfonamide

The racemic mixture of EXAMPLE 12A was resolved on a SFC chiral AD column to provide the title compound.

## Example 30B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2R)-1,4-dioxan-2-ylmethoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 30A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 2H), 8.35 (s, 1H), 8.03 (d, 2H), 7.48-7.57 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39

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(dd, 1H), 6.21 (s, 1H), 4.19-4.30 (m, 2H), 3.85-3.92 (m, 1H), 3.73-3.85 (m, 2H), 3.58-3.70 (m, 2H), 3.40-3.52 (m, 2H), 3.10 (s, 4H), 2.85 (s, 2H), 2.18-2.39 (m, 3H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 31

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 25A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.46 (m, 1H), 8.54 (m, 2H), 8.45 (m, 1H), 8.03 (d, 1H), 7.83 (m, 2H), 7.50 (m, 3H), 7.34 (m, 3H), 7.12 (m, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.11 (s, 2H), 3.79 (m, 4H), 3.51 (m, 6H), 3.05 (m, 4H), 2.17 (m, 3H), 1.17 (s, 6H).

## Example 32

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxan-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 12A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.37 (d, 1H), 8.03 (m, 2H), 7.50 (m, 3H), 7.37 (d, 2H), 7.13 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.25 (m, 2H), 4.12 (s, 2H), 3.84 (m, 3H), 3.63 (m, 2H), 3.45 (m, 2H), 3.06 (m, 4H), 2.86 (m, 2H), 2.24 (m, 6H), 1.20 (m, 6H).

## Example 33

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)cyclohexyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 9C, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.51 (d, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.76 (dd, 1H), 7.48 (m, 3H), 7.38 (d, 2H), 7.13 (d, 2H), 7.06 (d, 1H), 6.66 (dd, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 4.11 (s, 2H), 3.63 (m, 5H), 3.05 (m, 4H), 2.83 (s, 2H), 2.64 (m, 4H), 2.17 (m, 6H), 2.05 (m, 2H), 1.91 (s, 2H), 1.43 (m, 6H), 1.17 (m, 6H).

## Example 34

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 34A

(4-methoxycyclohexyl)methanamine

(4-Methoxyphenyl)methanamine (1 g, 1.29 mmol) in ethanol (10 ml) was treated with 5% Rh—Al<sub>2</sub>O<sub>3</sub> (99.8 mg, 0.048



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mmol) under H<sub>2</sub> atmosphere (500 psi) at 50° C. for 16 hours. Additional 5% Rh—Al<sub>2</sub>O<sub>3</sub> (0.4 g) was added. The resulting mixture was stirred under H<sub>2</sub> atmosphere (500 psi) at 60° C. for 2 hours. The insoluble material was filtered off and the filtrate was concentrated to provide a mixture of cis and trans product as an oil, which was used in the next step without further purification.

**Example 34B**

Trans-4-((4-methoxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (1.098 g) and EXAMPLE 34A (1 g) in tetrahydrofuran (20 mL) was treated with N,N-diisopropylethylamine (0.871 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase chromatography, and was eluted with 40-55% acetonitrile in 0.1% trifluoroacetic acid in water over 25 minutes.

**Example 34C**

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 34B in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.37 (s, 1H), 8.52-8.62 (m, 2H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47-7.55 (m, 3H), 7.34 (d, 2H), 7.02-7.09 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.21-3.27 (m, 5H), 3.02-3.12 (m, 5H), 2.75 (s, 2H), 2.20 (s, 4H), 2.14 (s, 2H), 1.93-2.04 (m, 4H), 1.79 (d, 2H), 1.55-1.65 (m, 1H), 1.38 (t, 2H), 0.97-1.12 (m, 4H), 0.92 (s, 6H).

**Example 35**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 36C, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.78 (s, 1H), 8.58 (s, 1H), 8.00 (d, 1H), 7.51 (m, 3H), 7.38 (d, 2H), 7.14 (d, 2H), 6.68 (dd, 1H), 6.37 (dd, 1H), 6.23 (d, 1H), 4.31 (d, 2H), 4.13 (s, 2H), 3.88 (dd, 2H), 3.11 (m, 5H), 2.16 (m, 6H), 1.65 (m, 2H), 1.35 (m, 2H), 1.19 (s, 6H).

**Example 36**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 36A**

5-Bromo-6-chloropyridine-3-sulfonyl chloride (8.2 g) in methanol (20 mL) was cooled to 0° C. To this solution was

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added 7N NH<sub>3</sub> in methanol (80 mL). The reaction mixture was stirred overnight. The solvent was removed at low temperature, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), filtered, and concentrated. The solid was purified by flash column chromatography on silica gel using 20-100% ethyl acetate in hexanes to give the title compound.

**Example 36B**

The title compound was prepared by substituting EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

**Example 36C**

A mixture of EXAMPLE 36B (0.702 g), dicyanozinc (0.129 g), and tetrakis(triphenylphosphine)palladium(0) (0.231 g) in N,N-dimethylformamide (2 mL) was degassed via vacuum/nitrogen cycle three times. The reaction mixture was heated at 120° C. for 3 hours. After cooling, it was poured into water and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 20%-60% ethyl acetate in hexanes to give the title compound.

**Example 36D**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 36C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.66 (s, 1H), 8.44 (s, 1H), 7.94 (d, 1H), 7.55 (d, 1H), 7.44 (t, 1H), 7.34-7.35 (m, 3H), 7.04 (d, 2H), 6.65 (dd, 1H), 6.32 (s, 1H), 6.24 (s, 1H), 4.26 (d, 2H), 3.86 (dd, 2H), 3.10 (s, 4H), 2.75 (s, 2H), 2.31-2.35 (m, 2H), 2.01-2.05 (m, 1H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.66 (m, 2H), 1.33-1.40 (m, 4H), 0.92 (s, 6H).

**Example 37**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(4-fluorotetrahydro-2H-pyran-4-ylmethoxy)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 37A**

1,6-dioxaspiro[2.5]octane-2-carbonitrile

A mixture of tetrahydropyran-4-one (10 mL) and chloroacetonitrile (6.4 mL) in tert-butanol (10 mL) was stirred for 10 minutes. To this solution was added a solution of potassium tert-butoxide (12.11 g) in 200 mL of tert-butanol at room temperature over 40 minutes. The reaction mixture was stirred for 16 hours, diluted with water and quenched slowly with 1 N HCl. The solvent was partially removed by rotary evaporation. It was then extracted with ether (5x200 mL). The combined extracts was washed with brine, dried over MgSO<sub>4</sub>,

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filtered, and the filtrate was concentrated and purified by flash chromatography on silica with 3:7 to 1:1 ethyl acetate:hexanes to provide the title compound.

## Example 37B

## 2-(4-fluorotetrahydro-2H-pyran-4-yl)-2-hydroxyacetonitrile

EXAMPLE 37A (11.5 g) in dichloromethane (40 mL) in a polypropylene bottle was treated with 70% hydrogen fluoride-pyridine (10.4 mL) dropwise at 0° C. The solution was allowed to warm to room temperature over 3 hours, and stirred for an additional 1.5 hours. The reaction mixture was diluted with ethyl acetate (200 mL) and poured into saturated aqueous NaHCO<sub>3</sub>. Additional solid NaHCO<sub>3</sub> was used carefully until bubbling ceased. The organic layer was isolated, and the aqueous layer was extracted with additional ethyl acetate three times (150 mL each). The combined organic layers were washed with 5% HCl (50 mL each, twice), brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give the desired product which was used directly in the next step.

## Example 37C

## (4-fluorotetrahydro-2H-pyran-4-yl)methanol

EXAMPLE 37B (11.7 g, 74 mmol) in 2-propanol (150 mL) and water (37.5 mL) was cooled to 0° C. To this solution was added NaBH<sub>4</sub> (4.20 g, 111 mmol). The solution was stirred and allowed to warm to room temperature over 3 hours. It was quenched with acetone, and stirred for another 1 hour. The clear liquid was separated from solid by decanting. Additional ethyl acetate (2×100 mL) was used to wash the solid, and the mixture was decanted. The combined organic solutions were concentrated. The residue was purified by flash chromatography, eluting with 1:1 ethyl acetate:hexanes to provide the title compound.

## Example 37D

## 4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 37E

## 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 37D in place of EXAMPLE 11B. <sup>1</sup>H NMR (dimethylsulfoxide-d<sub>6</sub>) 11.64 (s, 2H), 8.33 (s, 1H), 8.00-8.01 (m, 2H), 7.39-7.57 (m, 4H), 7.33 (d, J=8.24 Hz, 2H), 7.03 (d, J=8.54 Hz, 2H), 6.65 (dd, J=9.19 Hz, 1H), 6.37-6.38 (m, 1H), 6.19 (d, J=1.53 Hz, 1H), 4.35 (d, J=20.75 Hz, 2H), 3.74-3.78 (m, 2H), 3.55-3.60 (m, 2H), 3.07 (br, 4H), 2.80 (br, 2H), 2.25 (br, 4H), 2.13 (br, 2H), 1.81-1.94 (m, 6H), 1.38 (t, J=6.26 Hz, 2H), 0.91 (s, 6H).

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## Example 38

## N-([3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 38A

## 3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting 3-cyano-4-fluorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 38B

## 5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)benzamide

To a solution of EXAMPLE 38A (0.455 g) in ethanol (3 mL) and tetrahydrofuran (1 mL) was added hydrogen peroxide (30% in water, 2 mL) followed by 1 N aqueous NaOH (1.024 mL) and heated to 35° C. for 3 hours. The reaction was poured into dichloromethane (50 mL) and 1N aqueous HCl (25 mL). The aqueous layer was extracted with dichloromethane (3×50 mL). The precipitate contained in the combined organic layers was collected by filtration to give the title compound.

## Example 38C

## N-([3-(aminocarbonyl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 38B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.79-11.70 (m, 1H), 11.66-11.54 (m, 1H), 9.29-9.08 (m, 1H), 8.27 (d, 1H), 8.08 (d, 1H), 7.97-7.90 (m, 1H), 7.76-7.72 (m, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.50 (d, 1H), 7.39 (d, 1H), 7.23 (d, 1H), 7.08 (d, 1H), 6.74-6.67 (m, 1H), 6.44 (s, 1H), 6.22 (s, 1H), 4.03 (d, 6H), 3.74-3.52 (m, 4H), 3.33 (s, 4H), 3.11-2.90 (m, 2H), 2.01 (s, 4H), 1.79-1.58 (m, 2H), 1.24 (s, 5H), 0.94 (s, 6H).

## Example 39

## Cis-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-((4-morpholin-4-yl)cyclohexyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 39A

## Cis-tert-butyl-4-morpholinocyclohexylcarbamate

To a solution of morpholine (4.08 g) and tert-butyl 4-oxocyclohexylcarbamate (10 g) stirred for 24 hours at room temperature in titanium (IV) isopropoxide (27.5 mL), methanol (10 mL) was added followed by careful addition of

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sodium borohydride (3.55 g). The reaction mixture was quenched with water/NaOH solution, extracted with ether, dried over magnesium sulfate, filtered, and concentrated. The product was separated from the trans isomer and purified by flash chromatography (silica gel, 50%-100% acetone in hexanes) to provide the title compound.

**Example 39B**

cis-4-morpholinocyclohexanamine  
bis(2,2,2-trifluoroacetate)

To a solution of EXAMPLE 39A (2.43 g) in dichloromethane (15 ml) was added trifluoroacetic acid (5 ml) and the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was concentrated and the crude product was used without purification.

**Example 39C**

4-(cis-4-morpholinocyclohexylamino)-3-nitrobenzenesulfonamide

A solution of EXAMPLE 39B (0.40 g), 4-fluoro-3-nitrobenzenesulfonamide (0.478 g) and triethylamine (2 mL) in tetrahydrofuran (10 mL) was stirred for 3 days at room temperature. The reaction mixture was concentrated and purified by flash chromatography (silica gel, 0-30% methanol/dichloromethane) providing the product.

**Example 39D**

Cis-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 39C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.30 (d, 1H), 8.64 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.67 (t, 2H), 7.44 (d, 2H), 7.06 (d, 2H), 6.91 (d, 1H), 6.74 (dd, 1H), 6.48-6.55 (m, 2H), 3.65-3.73 (m, 5H), 3.02-3.09 (m, 4H), 2.76 (s, 2H), 2.41-2.48 (m, 4H), 2.25 (t, 2H), 2.09-2.16 (m, 5H), 1.97 (s, 2H), 1.77-1.86 (m, 2H), 1.55-1.63 (m, 6H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 40**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 40A**

5,6-dichloropyridine-3-sulfonamide

The title compound was prepared by substituting 5,6-dichloropyridine-3-sulfonyl chloride for 5-bromo-6-chloropyridine-3-sulfonyl chloride in EXAMPLE 36A.

**250****Example 40B**

5-chloro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

**Example 40C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 40B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.52 (s, 1H), 8.39 (d, 1H), 8.03 (d, 1H), 7.54 (d, 1H), 7.52 (d, 1H), 7.50 (dd, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.21 (d, 1H), 4.25 (d, 2H), 3.87 (dd, 2H), 3.30 (m, 2H), 3.10 (v br s, 4H), 2.90 (v br s, 2H), 2.35 (v br s, 4H), 2.17 (br m, 2H), 2.05 (m, 1H), 1.96 (s, 2H), 1.64 (d, 2H), 1.40 (t, 2H), 1.35 (ddd, 2H), 0.93 (s, 6H).

**Example 41**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 15H for EXAMPLE 3J and EXAMPLE 40B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.55 (d, 1H), 8.41 (d, 1H), 8.04 (d, 1H), 7.54 (m, 2H), 7.50 (dd, 1H), 7.38 (d, 2H), 7.14 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 4.25 (d, 2H), 4.12 (s, 2H), 3.87 (dd, 2H), 3.30 (m, 2H), 3.10 (v br s, 4H), 2.90 (v br s, 2H), 2.27 (v br s, 4H), 2.17 (br m, 2H), 2.05 (m, 1H), 1.96 (s, 2H), 1.64 (d, 2H), 1.35 (ddd, 2H), 0.97 (s, 6H).

**Example 42**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide

**Example 42A**

4-((tetrahydro-2H-pyran-4-yl)methylamino)-3-(trifluoromethyl)benzenesulfonamide

A mixture of 4-fluoro-3-(trifluoromethyl)benzenesulfonamide (1.056 g), (tetrahydro-2H-pyran-4-yl)methanamine (0.5 g) and N,N-diisopropylethylamine (1.68 g) in anhydrous dimethylsulfoxide (15 mL) solution was heated at 90° C. overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was

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washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound.

**Example 42B**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl]sulfonyl}benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 42A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.73 (s, 1H), 11.25 (s, 1H), 8.08 (d, 1H), 7.89 (d, 1H), 7.77 (m, 1H), 7.61 (d, 1H), 7.51 (m, 2H), 7.37 (d, 2H), 7.13 (d, 2H), 6.88 (d, 1H), 6.67 (dd, 1H), 6.53 (m, 1H), 6.43 (m, 1H), 6.15 (d, 1H), 4.11 (s, 2H), 3.82 (dd, 2H), 3.19 (m, 5H), 3.05 (m, 4H), 2.82 (s, 2H), 2.20 (m, 7H), 1.85 (m, 1H), 1.56 (m, 2H), 1.18 (s, 6H).

**Example 43**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)sulfonyl]phenyl}sulfonyl}benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 17A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.48 (m, 1H), 8.16 (d, 1H), 8.05 (d, 1H), 7.92 (dd, 1H), 7.52 (m, 3H), 7.37 (d, 2H), 7.27 (m, 1H), 7.11 (m, 3H), 6.68 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.11 (s, 2H), 3.84 (dd, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.84 (m, 2H), 2.23 (m, 5H), 1.84 (m, 1H), 1.55 (m, 2H), 1.25 (m, 3H), 1.18 (s, 6H).

**Example 44**

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 44A**

Trans-4-(4-morpholinocyclohexylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 16A by replacing 2-methoxyethanamine with EXAMPLE 9B.

**Example 44B**

Trans-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-(trifluoromethyl)sulfonyl}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 44A, respectively.

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<sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.62 (s, 1H), 8.08 (s, 1H), 8.00 (d, 1H), 7.85 (d, 1H), 7.47 (m, 3H), 7.38 (d, 2H), 7.14 (d, 2H), 6.98 (d, 1H), 6.65 (dd, 1H), 6.55 (m, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.12 (s, 2H), 3.54 (m, 6H), 3.04 (m, 4H), 2.83 (s, 2H), 2.57 (m, 3H), 2.24 (m, 6H), 1.91 (m, 5H), 1.34 (m, 4H), 1.20 (s, 6H).

**Example 45**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 45A**

4-(1-methylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 16A by replacing 2-methoxyethanamine with 1-methyl-4-aminopiperidine.

**Example 45B**

4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 15H and EXAMPLE 45A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.10 (s, 1H), 7.98 (d, 1H), 7.90 (dd, 1H), 7.49 (m, 3H), 7.39 (m, 3H), 7.14 (d, 2H), 7.02 (d, 1H), 6.65 (dd, 2H), 6.36 (dd, 1H), 6.22 (d, 1H), 4.12 (s, 2H), 3.75 (m, 1H), 3.16 (m, 4H), 2.98 (m, 5H), 2.88 (m, 5H), 2.67 (s, 2H), 2.22 (m, 6H), 1.68 (m, 1H), 1.18 (s, 6H).

**Example 46**

5-({4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}amino)sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide

5-sulfamoyl-2-((tetrahydro-2H-pyran-4-yl)methoxy)nicotinamide

To EXAMPLE 36C (0.025 g) in ethanol (1 mL) and tetrahydrofuran (1 mL) was added hydrogen peroxide (30% in water, 0.5 mL) followed by 1M aqueous sodium hydroxide (0.056 mL) then another 1 mL of tetrahydrofuran. The reaction was heated to 45° C. for 2 hours, cooled, quenched with 1N aqueous HCl (5 mL), and the product extracted into dichloromethane (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give the title compound.



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Example 46B

5-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl)-2-(tetrahydro-2H-pyran-4-ylmethoxy)nicotinamide

The title compound was prepared by substituting EXAMPLE 46A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.31-10.09 (m, 1H), 9.09 (s, 2H), 8.93-8.81 (m, 1H), 8.28-8.18 (m, 1H), 8.03-7.87 (m, 1H), 7.77-7.68 (m, 1H), 7.59-7.51 (m, 1H), 7.48-7.41 (m, 1H), 6.91 (d, 2H), 6.59-6.48 (m, 2H), 5.97 (s, 2H), 4.50 (d, 2H), 4.08-3.98 (m, 2H), 3.45 (s, 4H), 3.13-2.99 (m, 4H), 2.82-2.68 (m, 2H), 2.19 (s, 4H), 1.86 (s, 5H), 1.61-1.35 (m, 4H), 0.94 (s, 6H).

**Example 47**

N-({[5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 47A**

5-bromo-6-((1-methylpiperidin-4-yl)methoxy)pyridine-3-sulfonamide

To (1-methylpiperidin-4-yl)methanol (0.109 g) in tetrahydrofuran (2 mL) was added sodium hydride (0.136 g). After 30 minutes, EXAMPLE 36A (0.230 g) was added as a solution in tetrahydrofuran (1 mL) and the reaction was heated to 50° C. After 4 hours, the reaction was cooled, poured into water (10 mL) and dichloromethane (50 mL), and the pH was adjusted to pH-8. The aqueous layer was extracted with dichloromethane (3x50 mL), and the organic layers were combined, washed with brine (30 mL), dried over magnesium sulfate, filtered, and concentrated to give the title compound.

**Example 47B**

N-({[5-bromo-6-[(1-methylpiperidin-4-yl)methoxy]pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 47A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.51 (s, 1H), 8.35 (d, 1H), 8.17 (d, 1H), 7.93 (d, 1H), 7.60 (d, 1H), 7.44-7.40 (m, 1H), 7.33 (dd, 3H), 7.05 (d, 2H), 6.61 (d, 1H), 6.31 (dd, 1H), 6.24 (s, 1H), 4.25 (d, 2H), 3.40 (s, 4H), 3.01 (s, 4H), 2.73 (d, J=8.2, 5H), 2.20 (s, 6H), 1.93 (d, 4H), 1.54 (s, 1H), 1.39 (s, 2H), 1.24 (s, 2H), 0.93 (s, 6H).

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 48A**

4-((1-methylpiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1-methylpiperidin-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

**Example 48B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-[(1-methylpiperidin-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 48A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.54 (s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.87-7.77 (m, 1H), 7.58 (d, 1H), 7.43 (s, 1H), 7.40-7.00 (m, 7H), 6.70-6.56 (m, 1H), 6.31 (s, 1H), 6.24 (s, 1H), 4.05 (s, 2H), 3.46-3.33 (m, 2H), 3.02 (s, 6H), 2.72 (d, 5H), 2.21 (s, 6H), 1.96 (s, 5H), 1.70-1.48 (m, 2H), 1.39 (s, 2H), 0.93 (s, 6H).

**Example 49**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl})-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 49A**

6-((1,4-dioxan-2-yl)methoxy)-5-bromopyridine-3-sulfonamide

The title compound was prepared by substituting (1,4-dioxan-2-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

**Example 49B**

6-((1,4-dioxan-2-yl)methoxy)-5-cyanopyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 49A for EXAMPLE 36B in EXAMPLE 36C.

**Example 49C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-cyano-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl})-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 49B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H

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NMR (400 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.50 (s, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 7.91 (d, 1H), 7.58 (d, 1H), 7.42 (t, 1H), 7.35 (d, 2H), 7.28 (s, 1H), 7.06 (d, 2H), 6.64 (dd, 1H), 6.29 (m, 2H), 4.40 (d, 2H), 3.90 (m, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 3.46 (m, 4H), 3.07 (s, 4H), 2.85 (m, 2H), 2.34 (m, 4H), 2.16 (m, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

**Example 50**

N-([5-bromo-6-(1,4-dioxan-2-ylmethoxy)pyridin-3-yl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 49A for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (400 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.60 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 7.99 (d, 1H), 7.56 (d, 1H), 7.46 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.65 (dd, 1H), 6.36 (dd, 1H), 6.22 (d, 1H), 4.34 (m, 2H), 3.88 (m, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 3.46 (m, 2H), 3.06 (s, 4H), 2.81 (s, 2H), 2.26 (m, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.38 (m, 2H), 0.93 (s, 6H).

**Example 51**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 51A**

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with (2,2-dimethyltetrahydro-2H-pyran-4-yl)methanol.

**Example 51B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-([2,2-dimethyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 51A in place of EXAMPLE 11B.  $^1\text{H}$  NMR (400 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.69 (s, 2H), 8.35 (s, 2H), 8.03 (d, 4H), 7.47-7.58 (m, 6H), 7.31-7.42 (m, 6H), 7.04 (d, 4H), 6.68 (dd, 2H), 6.40 (s, 2H), 6.20 (d, 2H), 3.96-4.09 (m, 2H), 3.54-3.68 (m, 2H), 3.09 (s, 4H), 2.83 (s, 2H), 2.09-2.37 (m, 7H), 1.96 (s, 2H), 1.55-1.69 (m, 2H), 1.39 (t, 2H), 1.19 (m, 8H), 0.92 (s, 6H).

**Example 52**

N-([3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 52A**

3-cyano-4-fluorobenzene sulfonamide

3-Cyano-4-fluorobenzene-1-sulfonyl chloride (1.1 g) in 1,4-dioxane (10 mL) at 0° C. was treated dropwise with a 7 M

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ammonia solution in methanol (3.57 mL) and stirred for 30 minutes. A small amount of solid was removed by filtration and discarded. The filtrate was concentrated, diluted with ethyl acetate, washed with water and brine, dried ( $\text{MgSO}_4$ ), filtered, concentrated and triturated with diethyl ether to give the product.

**Example 52B**

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 52A for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

**Example 52C**

3-chloro-5-cyano-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

EXAMPLE 52B (0.148 g) in acetonitrile (5 mL) was treated with N-chlorosuccinimide (0.080 g), heated at 60° C. for 3 hours and filtered to remove a small amount of solid. The filtrate was concentrated and chromatographed on silica gel with 3-15% ethyl acetate in dichloromethane as eluent. The obtained solid was slurried in water, filtered, rinsed with additional water and dried under vacuum to give the product.

**Example 52D**

N-([3-chloro-5-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 52C for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.70 (s, 1H), 11.41 (br s, 1H), 8.07 (d, 1H), 7.89 (s, 2H), 7.61 (m, 1H), 7.53 (m, 2H), 7.35 (d, 2H), 7.18 (m, 1H), 7.05 (d, 2H), 6.69 (m, 1H), 6.42 (dd, 1H), 6.18 (dd, 1H), 3.83 (m, 2H), 3.55 (t, 2H), 3.23 (m, 3H), 3.06 (m, 4H), 2.15 (m, 4H), 1.92 (m, 4H), 1.60 (m, 2H), 1.40 (m, 2H), 1.19 (m, 4H), 0.93 (s, 6H).

**Example 53**

N-([4-[(1-acetyl)piperidin-4-yl]amino]-3-nitrophenyl]sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 53A**

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 1G.

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## Example 53B

N-({4-[(1-acetylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A 5 mL round-bottomed flask was charged with EXAMPLE 53A (120 mg), 1-acetylpiperidin-4-amine (28 mg), and triethylamine (0.064 mL) in dioxane (2 mL). The reaction mixture was heated to 90° C. for 24 hours. The reaction mixture was cooled to room temperature, and added to a silica gel column and purified by eluting with 0-5% methanol in dichloromethane. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (br s, 1H), 8.65 (d, 1H), 8.24 (d, 1H), 8.03 (d, 1H), 7.83 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.19 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 4.28 (d, 1H), 3.97-3.75 (m, 2H), 3.07 (br s, 4H), 2.87-2.70 (m, 4H), 2.29-2.10 (m, 6H), 2.02 (s, 3H), 2.00-1.89 (m, 4H), 1.66-1.54 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

## Example 54

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 54A

2-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 2-chloro-4,5-difluorobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 54

N-({2-chloro-5-fluoro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 54A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.76 (s, 1H), 11.31 (s, 1H), 8.08 (d, 1H), 7.69 (d, 1H), 7.60 (d, 1H), 7.55 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 (s, 1H), 6.84 (d, 1H), 6.69 (dd, 1H), 6.45 (dd, 1H), 6.13 (d, 1H), 3.82 (dd, 2H), 3.24 (t, 2H), 3.05 (m, 6H), 2.73 (s, 2H), 2.14 (m, 6H), 1.95 (s, 2H), 1.81 (m, 1H), 1.61 (m, 2H), 1.38 (t, 2H), 1.17 (m, 2H), 0.92 (s, 6H).

## Example 55

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 2A for

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EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (br s, 1H), 8.75 (t, 1H), 8.54 (d, 1H), 8.03 (d, 1H), 7.79 (dd, 1H), 7.54-7.48 (m, 3H), 7.35 (d, 2H), 7.08-7.02 (m, 3H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 3.61 (t, 4H), 3.43 (q, 2H), 3.29 (m, 2H), 3.06 (br s, 4H), 2.73 (br s, 2H), 2.47 (br s, 4H), 2.18 (m, 6H), 1.95 (br s, 2H), 1.80 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 56

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 56A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 37C for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 56B

The title compound was prepared by substituting EXAMPLE 56A for EXAMPLE 36B in EXAMPLE 36C.

## Example 56C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 56B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.70 (s, 1H), 8.51 (s, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.45 (t, 1H), 7.35-7.37 (m, 3H), 7.06 (d, 2H), 6.67 (dd, 1H), 6.33 (d, 1H), 6.26 (s, 1H), 4.56 (d, 2H), 3.76-3.80 (s, 2H), 3.56-3.62 (m, 2H), 3.01-3.10 (m, 4H), 2.14-2.18 (m, 2H), 1.96 (s, 2H), 1.80-1.87 (m, 4H), 1.41 (t, 2H), 0.93 (s, 6H).

## Example 57

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 57A

5-bromo-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-morpholinoethanol for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

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## Example 57B

5-cyano-6-(2-morpholinoethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 57A for EXAMPLE 36A in EXAMPLE 36B.

## Example 57C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(2-morpholin-4-ylethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 57B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 7.92 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.36 (d, 2H), 7.31 (s, 1H), 7.06 (d, 2H), 6.65 (dd, 1H), 6.31 (d, 1H), 6.27 (d, 1H), 4.59 (t, 2H), 3.59 (s, 4H), 3.08 (s, 4H), 2.89 (s, 2H), 2.65 (s, 4H), 2.16-2.18 (m, 2H), 1.97 (s, 2H), 1.41 (t, 2H), 0.93 (s, 6H).

## Example 58

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 58A

3-chloro-4-(2-(2-methoxyethoxy)ethylthio)benzenesulfonamide

In a 25 mL microwave tube was added sodium hydride (0.6 g) in tetrahydrofuran (10 mL) to give a suspension. 2-(2-Methoxyethoxy)ethanethiol (1 g) was added slowly. After stirring for 30 minutes, 3-chloro-4-fluorobenzenesulfonamide (1.54 g) dissolved in 10 mL tetrahydrofuran was added slowly. The mixture was heated at 110° C. for 30 minutes in a Biotage Initiator microwave reactor. Water was added, the product was extracted with ether (20 mL×3), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica eluting with 0-25% ethyl acetate in hexane.

## Example 58B

3-chloro-4-(2-(2-methoxyethoxy)ethylsulfonyl)benzenesulfonamide

EXAMPLE 58A (0.15 g) was suspended in acetic acid (3 mL). Peracetic acid (0.4 mL) was added slowly. The mixture was stirred at room temperature overnight, then poured into Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, and the product precipitated. After filtration and washing with water, the product was dried under vacuum.

## Example 58C

N-[(3-chloro-4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 58B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H

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NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.52 (s, 1H), 7.92 (d, 1H), 7.84 (m, 2H), 7.68 (m, 1H), 7.62 (d, 1H), 7.42 (t, 1H), 7.35 (d, 2H), 7.29 (m, 1H), 7.05 (d, 2H), 6.62 (dd, 1H), 6.32 (m, 1H), 6.26 (d, 1H), 3.74 (t, 2H), 3.68 (t, 2H), 3.24 (m, 2H), 3.06 (m, 5H), 3.01 (m, 4H), 2.74 (s, 2H), 2.19 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 59

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 59A

4-(2-(2-methoxyethoxy)ethylthio)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 3-chloro-4-fluorobenzenesulfonamide in EXAMPLE 58A.

## Example 59B

4-(2-(2-methoxyethoxy)ethylsulfonyl)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 59A for EXAMPLE 58A in EXAMPLE 58B.

## Example 59C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 59B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.51 (s, 1H), 8.17 (m, 1H), 7.94 (m, 3H), 7.64 (d, 1H), 7.42 (m, 1H), 7.35 (d, 2H), 7.28 (d, 1H), 7.05 (d, 2H), 6.62 (m, 1H), 6.28 (m, 2H), 3.83 (m, 4H), 3.16 (m, 2H), 3.08 (s, 3H), 3.01 (m, 4H), 2.73 (s, 2H), 2.18 (m, 6H), 1.96 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H)

## Example 60

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(2-methoxyethoxy)ethyl]sulfonyl}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 60A

Trans-4-(4-aminocyclohexyloxy)-3-nitrobenzenesulfonamide

To a solution of tert-butyl 4-hydroxycyclohexylcarbamate (0.250 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.186 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.256 g) was added as a solution in tetrahydrofuran (1 mL). The reaction was heated to 60° C. for 1.5 hours, cooled, and poured into a mixture of dichloromethane (100 mL) and water (25 mL). The aqueous layer was adjusted to pH~4 with 1N aqueous HCl and the organic



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layer was separated, washed with brine (50 ml), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (GraceResolv 40 g) and eluted using a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes. This solid was treated with HCl (4.0M in dioxane, 5 ml) at room temperature for 1 hour and concentrated to give the title compound.

## Example 60B

4-(trans-4-morpholinocyclohexyloxy)-3-nitrobenzenesulfonamide

To EXAMPLE 60A (0.220 g) and 1-bromo-2-(2-bromoethoxy)ethane (0.177 g) in N,N-dimethylformamide (3 mL) was added triethylamine (0.338 ml) and the reaction heated to 70° C. for 5 hours. The reaction was cooled and the resulting precipitate was removed by filtration. The reaction was concentrated and loaded onto silica gel and was eluted using a gradient of 0.5% to 7.5% methanol/dichloromethane to give the title compound.

## Example 60C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 60B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.62 (s, 1H), 8.23 (s, 1H), 7.99 (s, 1H), 7.96-7.88 (m, 1H), 7.54 (d, 1H), 7.48 (s, 2H), 7.34 (d, 3H), 7.04 (d, 2H), 6.72-6.58 (m, 1H), 6.37 (s, 1H), 6.21 (s, 1H), 4.69-4.47 (m, 1H), 3.66 (s, 4H), 3.05 (s, 4H), 2.76 (s, 6H), 2.22 (s, 9H), 1.96 (s, 4H), 1.39 (s, 6H), 0.92 (s, 6H).

## Example 61

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 61A

5-bromo-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ylamino)pyridine-3-sulfonamide

A mixture of EXAMPLE 36A (1.0 g), EXAMPLE 3L (0.95 g) and triethylamine (3.08 mL) in anhydrous dioxane (20 mL) was heated at 110° C. overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 2%-8% methanol/dichloromethane to give the title compound.

## Example 61B

N-({5-bromo-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}pyridin-3-yl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 61A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H

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NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.35 (s, 1H), 8.00 (s, 2H), 7.55 (d, 1H), 7.46 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.63 (dd, 1H), 6.49 (m, 1H), 6.36 (s, 1H), 6.20 (s, 1H), 4.05 (m, 1H), 3.94 (d, 2H), 3.28 (m, 6H), 3.01 (s, 4H), 2.72 (s, 2H), 2.16 (m, 6H), 1.93 (m, 4H), 1.80 (m, 4H), 1.57 (m, 2H), 1.38 (t, 2H), 1.17 (t, 2H), 0.90 (s, 6H).

## Example 62

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 62A

4-(2-cyanoethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 3-amino-propanenitrile for EXAMPLE 39B in EXAMPLE 39C.

## Example 62B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(2-cyanoethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 62A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (501 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 9.24 (d, 1H), 9.04 (t, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.13 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (ddd, 2H), 7.07 (ddd, 2H), 7.02 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 6.48 (dd, 1H), 3.83 (q, 2H), 3.07 (d, 4H), 2.98 (t, 2H), 2.77 (s, 2H), 2.26 (s, 2H), 2.11-2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 63

Cis-4-(4-{[4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylcyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 15H for EXAMPLE 3J and EXAMPLE 39C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (501 MHz, pyridine-d<sub>5</sub>) δ 13.09 (s, 1H), 9.30 (d, 1H), 8.64 (d, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.10 (d, 1H), 7.68 (dt, 2H), 7.46 (ddd, 2H), 7.12 (ddd, 2H), 6.91 (d, 1H), 6.72 (dd, 1H), 6.51 (dd, 1H), 6.49 (d, 1H), 5.69 (s, 2H), 4.40 (s, 2H), 3.69-3.73 (m, 4H), 3.68 (s, 1H), 2.95-3.02 (m, 4H), 2.84 (s, 2H), 2.40-2.46 (m, 4H), 2.21 (s, 2H), 2.08-2.15 (m, 5H), 1.76-1.84 (m, 2H), 1.55-1.63 (m, 6H), 1.29 (s, 6H).

## Example 64

Trans-N-({4-({4-[bis(cyclopropylmethyl)amino]cyclohexyl}amino)-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 64A

tert-butyl(trans)-4-(bis(cyclopropylmethyl)amino)cyclohexylcarbamate

The title compound was prepared by substituting cyclopropanecarbaldehyde for 4'-chlorobiphenyl-2-carboxaldehyde

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and tert-butyl(trans)-4-aminocyclohexylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 64B

(trans)-N<sup>1</sup>,N<sup>1</sup>-bis(cyclopropylmethyl)cyclohexane-1,4-diamine dihydrochloride

To a solution of EXAMPLE 64A (1.4 g) in dichloromethane (10 ml) was added hydrogen chloride (10 ml, 4M in dioxane) and the reaction was stirred for 16 hours at room temperature. The reaction mixture was diluted with ether and pure product was filtered off.

## Example 64C

Trans-4-(4-(bis(cyclopropylmethyl)amino)cyclohexylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 64B for EXAMPLE 39B in EXAMPLE 39C.

## Example 64D

Trans-N-([4-([4-bis(cyclopropylmethyl)amino]cyclohexyl)amino]-3-nitrophenyl)sulfonyl]-4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 64C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.30 (d, 1H), 8.44 (d, 1H), 8.41 (dd, 1H), 8.37 (d, 1H), 8.12 (d, 1H), 7.67 (d, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.00 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 3.36-3.43 (m, 1H), 3.02-3.09 (m, 4H), 2.87-2.94 (m, 1H), 2.77 (s, 2H), 2.47 (d, 4H), 2.25 (t, 2H), 2.11-2.16 (m, 4H), 2.08 (d, 2H), 1.97 (s, 2H), 1.84 (d, 2H), 1.39 (t, 2H), 1.26-1.35 (m, 4H), 0.90-0.98 (m, 8H), 0.50-0.56 (m, 4H), 0.18-0.23 (m, 4H).

## Example 65

4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-methylpiperidin-4-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 65A

4-((1-methylpiperidin-4-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-aminomethyl-1-methyl piperidine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 65B

4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1-methylpiperidin-4-yl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 65A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, dichloromethane-d<sub>2</sub>) δ 9.57 (bs, 1H),

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8.78 (d, 1H), 8.41 (d, 1H), 8.14 (d, 1H), 7.90 (m, 2H), 7.64 (d, 1H), 7.45 (d, 1H), 7.23 (d, 2H), 6.95 (d, 2H), 6.76 (d, 1H), 6.59 (dd, 1H), 6.51 (d, 1H), 6.09 (d, 1H), 3.21 (m, 2H), 3.08 (m, 4H), 3.02 (m, 2H), 2.74 (s, 2H), 2.33 (s, 3H), 2.21-2.17 (m, 6H), 2.16-2.02 (m, 3H), 1.97 (br.s, 2H), 1.78 (m, 4H), 1.41 (t, 2H), 0.94 (s, 6H).

## Example 66

4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([morpholin-3-ylmethyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 66A

tert-butyl 3-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 66B

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 66A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1F, with the exception that the product was purified on a silica gel column eluted with 4% methanol in dichloromethane.

## Example 66C

4-(4-[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([morpholin-3-ylmethyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A solution of EXAMPLE 66B in 50% trifluoroacetic acid and dichloromethane mixture was stirred at ambient temperature for 2 hours. The solvents were evaporated and the residue was purified on a reverse phase HPLC using a gradient of 20-80% acetonitrile in water containing 10 mM ammonium acetate. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (s, 1H), 8.52 (bs, 1H), 8.49 (d, 1H), 7.98 (d, 1H), 7.78 (d, 1H), 7.54 (d, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 7.34 (d, 2H), 7.04 (m, 3H), 6.65 (dd, 1H), 6.34 (s, 1H), 6.21 (d, 1H), 3.89 (d, 1H), 3.76 (d, 1H), 3.55-3.46 (m, 2H), 3.40-3.35 (m, 4H), 3.04 (m, 4H), 2.91 (t, 1H), 2.73 (s, 2H), 2.20-2.12 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 67

4-(4-[2-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl]methyl)piperazin-1-yl)-N-([4-([4-methylpiperazin-1-yl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE

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1F with EXAMPLE 15H and EXAMPLE 6A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 9.04 (s, 1H), 8.44 (d, 1H), 7.97 (d, 1H), 7.76 (dd, 1H), 7.49 (m, 4H), 7.38 (d, 2H), 7.14 (d, 2H), 6.64 (dd, 1H), 6.34 (d, 1H), 6.21 (d, 1H), 4.12 (s, 2H), 3.03 (m, 6H), 2.85 (m, 5H), 2.29 (m, 4H), 2.18 (m, 6H), 1.20 (s, 6H).

**Example 68**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 68A****4-morpholinobut-2-yn-1-ol**

To a solution of morpholine (4.36 g) in toluene (15 mL) was added 4-chlorobut-2-yn-1-ol (2.09 g) in toluene (5 mL). The solution was stirred at 85° C. for 3 hours. After cooling, the solid was filtered off. The filtrate was subjected to vacuum distillation to give the pure title compound.

**Example 68B****4-(4-morpholinobut-2-ynyloxy)-3-nitrobenzene-sulfonamide**

The title compound was prepared by substituting EXAMPLE 68A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

**Example 68C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-ylbut-2-ynyl)oxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 68B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.36 (s, 1H), 8.08 (d, 1H), 8.03 (d, 1H), 7.47-7.53 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 5.15 (s, 2H), 3.52-3.55 (m, 4H), 3.09 (s, 4H), 2.84 (br s, 2H), 2.23-2.40 (m, 6H), 2.12-2.18 (m, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

**Example 69**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 69A**

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-((triisopropylsilyl)ethynyl)pyridine-3-sulfonamide

Example 36B (0.176 g), bis(triphenylphosphine)palladium(II) chloride (0.176 g), copper(I) iodide (0.010 g), N,N-dimethylacetamide (2.5 mL) and triethylamine (0.105 mL) were combined, flushed with nitrogen and stirred for 2 minutes. (Triisopropylsilyl)acetylene (0.135 mL) was added and

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the reaction mixture was flushed with nitrogen again, heated at 60° C. overnight, diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 10-30% ethyl acetate in hexanes as the eluent to give the product.

**Example 69B**

5-ethynyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

Example 69A (0.205 g) in tetrahydrofuran (3 mL) at ambient temperature was treated with tetrabutyl ammonium fluoride (1 M in tetrahydrofuran, 0.906 mL) and stirred at ambient temperature for 4 hours. Additional tetrabutyl ammonium fluoride (1 M in tetrahydrofuran, 1.8 mL) was added and the mixture was heated at 40° C. for 45 minutes. Solid tetrabutyl ammonium fluoride (0.253 g) was added and heating was continued for 30 minutes. The reaction mixture was concentrated and then chromatographed on silica gel using 0-2% methanol in dichloromethane as the eluent to give the product.

**Example 69**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[5-ethynyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 69B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.58 (d, 1H), 8.19 (d, 1H), 8.05 (d, 1H), 7.53 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.56 (s, 1H), 4.24 (d, 2H), 3.87 (dd, 2H), 3.38 (m, 3H), 3.07 (m, 4H), 2.86 (m, 2H), 2.29 (m, 5H), 2.04 (m, 3H), 1.64 (dd, 2H), 1.34 (m, 4H), 0.93 (s, 6H).

**Example 70**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 70A****4-amino-3-cyanobenzenesulfonamide**

3-Cyano-4-fluorobenzene-1-sulfonyl chloride (1.1 g) was dissolved in dioxane (4 mL). The solution was cooled to 0° C. and 7 mL of an ammonia (7N in methanol) solution was added. After the addition was complete, the ice bath was removed and the reaction was stirred at room temperature for 24 hours. After concentration of the reaction mixture, the crude material was purified by flash chromatography eluting with a gradient of 30-100% ethyl acetate/hexanes.

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## Example 70B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-amino-3-cyanophenylsulfonyl)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 70A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.

## Example 70C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-amino-3-carbamoylphenylsulfonyl)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzamide

To a solution of EXAMPLE 70B (90 mg) in ethanol (2 mL) was added tetrahydrofuran (2 mL), hydrogen peroxide (30%, 1 mL) and 1M sodium hydroxide solution (0.48 mL), followed by an additional 2 mL of tetrahydrofuran. The reaction was heated to 45° C. for 30 minutes, cooled, and then quenched with 5% HCl solution and extracted twice with dichloromethane. The extracts were combined and concentrated to obtain the product.

## Example 70D

4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-oxo-3,4-dihydroquinazolin-6-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 70C (80 mg) was combined with trimethyl orthoformate (2.3 mL) and trifluoroacetic acid (0.03 mL) and the resulting solution was stirred at room temperature for 4 hours. The mixture was purified by flash chromatography, eluting with a gradient of 3-10% methanol/dichloromethane. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 12.61 (s, 1H), 11.71 (s, 1H), 8.65 (d, 1H), 8.24 (s, 1H), 8.17 (dd, 1H), 8.04 (m, 1H), 7.73 (d, 1H), 7.57 (d, 1H), 7.51 (m, 2H), 7.39 (d, 2H), 7.07 (d, 2H), 6.70 (dd, 1H), 6.40 (m, 1H), 6.24 (br s, 1H), 3.61 (m, 6H), 3.03 (m, 2H), 2.75 (m, 2H), 2.17 (m, 2H), 2.01 (m, 2H), 1.44 (m, 2H), 0.94 (s, 6H).

## Example 71

Trans-4-((4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)-N-((4-((4-morpholin-4-ylcyclohexyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 71A

8-chlorospiro[4.5]dec-7-ene-7-carbaldehyde

To a solution of N,N-dimethylformamide (2.81 mL) in dichloromethane (40 mL) was added dropwise POCl<sub>3</sub> (2.78 mL) at 0° C. The reaction mixture was warmed up to room temperature and spiro[4.5]decan-8-one (3.95 g) in dichloromethane (5 mL) was added dropwise. The mixture was stirred overnight. The reaction was quenched with cold aqueous sodium acetate and the resulting mixture was extracted with ether and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

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## Example 71B

8-(4-chlorophenyl)spiro[4.5]dec-7-ene-7-carbaldehyde

To a suspension of EXAMPLE 71A (3 g) in water (50 mL) was added 4-chlorophenylboronic acid (2.83 g), tetrabutylammonium (4.87 g), potassium carbonate (6.26 g) and palladium(II) acetate (0.169 g). The reaction mixture was stirred at 45° C. for 5 hours and extracted with dichloromethane. The organic layer was concentrated and the residue was loaded onto a silica gel column, and eluted with 5-20% ethyl acetate in hexane to give the title compound.

## Example 71C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 71B (274 mg) in dichloroethane (3.5 mL) was added EXAMPLE 15F (387 mg) and sodium triacetoxymethylborohydride (317 mg). The reaction mixture was stirred overnight. Sodium cyanoborohydride (37.6 mg) was added and the resulting mixture stirred overnight. The reaction was quenched with water and diluted with dichloromethane. The mixture was washed with water extensively and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

## Example 71D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 3J using EXAMPLE 71C in place of EXAMPLE 3I.

## Example 71E

Trans-4-((4-((8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl)methyl)piperazin-1-yl)-N-((4-((4-morpholin-4-ylcyclohexyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 9C in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.51 (s, 1H), 8.15 (d, 1H), 8.01 (d, 1H), 7.76 (d, 1H), 7.44-7.53 (m, 3H), 7.34 (d, 2H), 7.07 (d, 3H), 6.66 (dd, 1H), 6.37 (dd, 1H), 6.20 (d, 1H), 3.50-3.70 (m, 5H), 3.04 (s, 4H), 2.55-2.76 (m, 5H), 2.34-2.39 (m, 1H), 2.20 (d, 6H), 2.03 (s, 4H), 1.91 (s, 2H), 1.61 (q, 4H), 1.51 (t, 2H), 1.36-1.46 (m, 8H).

## Example 72

Cis-4-((4-((4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)-N-((4-((4-methoxycyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 15H and 29A in place of



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EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.45 (s, 1H), 8.59 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.54 (d, 1H), 7.47-7.52 (m, 2H), 7.37 (d, 2H), 7.13 (d, 2H), 7.08 (d, 1H), 6.68 (dd, 1H), 6.35-6.42 (m, 1H), 6.19 (d, 1H), 4.11 (s, 2H), 3.37 (s, 1H), 3.26 (t, 2H), 3.20 (s, 3H), 3.07 (s, 4H), 2.83 (s, 2H), 2.17 (d, 6H), 1.81 (dd, 2H), 1.64-1.73 (m, 1H), 1.48 (dd, 2H), 1.23-1.41 (m, 4H), 1.18 (s, 6H).

## Example 73

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 37D in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.37 (s, 1H), 7.98-8.11 (m, 2H), 4.38 (d, 2H), 3.74-3.82 (m, 2H), 3.54-3.64 (m, 2H), 3.44 (s, 1H), 3.08 (s, 3H), 2.58-2.89 (m, 2H), 2.13-2.35 (m, 4H), 2.04 (s, 2H), 1.78-1.93 (m, 4H), 1.57-1.65 (m, 4H), 1.52 (t, 2H), 1.36-1.47 (m, 4H).

## Example 74

Trans-4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 34B in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.39 (s, 1H), 8.58 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47-7.55 (m, 3H), 7.34 (d, 2H), 7.07 (d, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.25 (t, 2H), 3.22 (s, 3H), 3.06 (s, 5H), 2.71 (s, 2H), 2.21 (s, 6H), 1.94-2.06 (m, 4H), 1.79 (d, 2H), 1.57-1.65 (m, 5H), 1.51 (t, 2H), 1.39 (t, 4H), 0.95-1.11 (m, 4H).

## Example 75

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 75A

methyl 5,5-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

The title compound was prepared by substituting 4,4-dimethyl-2-methoxycarbonylcyclohexanone for 5,5-dimethyl-2-methoxycarbonylcyclohexanone in EXAMPLE 3A.

## Example 75B

methyl 2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 75A for EXAMPLE 3A in EXAMPLE 3B.

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## Example 75C

(2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methanol

The title compound was prepared by substituting EXAMPLE 75B for EXAMPLE 3B in EXAMPLE 3C.

## Example 75D

2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enecarbaldehyde

To a solution of EXAMPLE 75C (2.8 g) in dichloromethane (50 mL) was added Dess-Martin Periodinane (5.68 g). The reaction mixture was stirred at room temperature for 3 hours and diluted with ether and washed with 5% NaOH and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography using 20% ethyl acetate in hexanes to provide the title compound.

## Example 75E

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by replacing 4'-chlorobiphenyl-2-carboxaldehyde with EXAMPLE 75D and tert-butyl piperazine-1-carboxylate with EXAMPLE 15F in EXAMPLE 1A.

## Example 75F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared as described in EXAMPLE 15H by replacing EXAMPLE 15G with EXAMPLE 75E.

## Example 75G

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 75F and EXAMPLE 1F in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47-7.55 (m, 3H), 7.31-7.36 (m, 2H), 7.05-7.13 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.18 (d, 1H), 3.85 (dd, 2H), 3.22-3.31 (m, 4H), 3.07 (s, 4H), 2.67-2.78 (m, 2H), 2.19 (s, 6H), 1.82-1.98 (m, 3H), 1.56-1.66 (m, 2H), 1.39 (t, 2H), 1.17-1.33 (m, 3H), 0.93 (s, 6H).

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## Example 76

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-cyano-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 75F and EXAMPLE 36C in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.62 (s, 1H), 8.73 (s, 1H), 8.52 (s, 1H), 7.98 (d, 1H), 7.56 (d, 1H), 7.45-7.51 (m, 1H), 7.43 (s, 1H), 7.37 (d, 2H), 7.10 (d, 2H), 6.68 (dd, 1H), 6.35 (dd, 1H), 6.25 (s, 1H), 4.29 (d, 2H), 3.88 (dd, 2H), 3.12 (d, 4H), 2.21 (s, 2H), 2.00-2.11 (m, 1H), 1.95 (s, 2H), 1.64 (dd, 2H), 1.27-1.46 (m, 4H), 0.95 (s, 6H)

## Example 77

tert-butyl 3-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl]-2-nitrophenoxy]methyl}morpholine-4-carboxylate

## Example 77A

tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with tert-butyl 3-(hydroxymethyl)morpholine-4-carboxylate.

## Example 77B

tert-butyl 3-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl]-2-nitrophenoxy]methyl}morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 77A in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.36 (s, 1H), 8.01-8.11 (m, 2H), 7.47-7.61 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.20 (s, 1H), 4.41-4.52 (m, 2H), 4.15-4.28 (m, 1H), 3.59-3.95 (m, 3H), 3.51 (d, 1H), 3.34-3.43 (m, 1H), 3.10 (s, 5H), 2.84 (s, 2H), 2.28 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.20-1.45 (m, 12H), 0.92 (s, 6H).

## Example 78

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(morpholin-3-ylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 77B (100 mg) in dichloromethane (10 mL) at 0° C. was treated with trifluoroacetic acid (5 mL) for 20 minutes. The reaction mixture was concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 35-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoro-

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roacetic acid salt was dissolved in dichloromethane (10 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.23 (d, 1H), 7.94 (d, 1H), 7.90 (dd, 1H), 7.57 (d, 1H), 7.42-7.46 (m, 1H), 7.31-7.37 (m, 3H), 7.25 (d, 1H), 7.01-7.09 (m, 2H), 6.64 (dd, 1H), 6.29-6.37 (m, 1H), 6.24 (d, 1H), 4.17-4.31 (m, 2H), 3.90-4.05 (m, 1H), 3.77-3.85 (m, 1H), 3.45-3.59 (m, 4H), 2.94-3.13 (m, 6H), 2.76 (s, 2H), 2.18 (d, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 79

4-(4-{[8-(4-chlorophenyl)spiro[4.5]dec-7-en-7-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 71D and EXAMPLE 1F in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.77-7.84 (m, 1H), 7.45-7.56 (m, 3H), 7.34 (d, 2H), 7.04-7.13 (m, 3H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.85 (dd, 2H), 3.22-3.31 (m, 4H), 3.07 (s, 4H), 2.71 (s, 2H), 2.21 (s, 6H), 2.03 (s, 2H), 1.81-1.94 (m, 1H), 1.56-1.68 (m, 6H), 1.51 (t, 2H), 1.34-1.45 (m, 4H), 1.20-1.33 (m, 2H).

## Example 80

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[1-(methylsulfonyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 1-(methylsulfonyl)piperidin-4-amine for 1-acetyl piperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (br s, 1H), 8.57 (d, 1H), 8.25 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 3.80 (m, 1H), 3.57 (m, 2H), 3.08 (br s, 4H), 2.95 (td, 2H), 2.92 (s, 3H), 2.85-2.72 (m, 2H), 2.30-2.10 (m, 6H), 2.07-1.93 (m, 4H), 1.70 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 81

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxido-tetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 81A

1,1-Dioxotetrahydro-2H-thiopyran-4-amine

N-Benzyl-1,1-dioxotetrahydro-2H-thiopyran-4-amine (2.00 g) was added to ethanol (40 mL) in a pressure bottle. Palladium hydroxide on carbon (0.587 g.) was added and the solution was stirred under 30 psi of hydrogen at room tem-

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perature for 2 hours. The mixture was filtered through a nylon membrane and the solvent was removed under vacuum.

## Example 81B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-dioxido-tetrahydro-2H-thiopyran-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 81A for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (br s, 1H), 8.55 (d, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.86 (dd, 1H), 7.52-7.47 (m, 3H), 7.35 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.21 (d, 1H), 4.05 (m, 1H), 3.22-3.00 (m, 8H), 2.79 (br s, 2H), 2.31-2.11 (m, 10H), 1.96 (br s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 82

N-[(4-chloro-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and 4-chloro-3-nitrobenzenesulfonamide for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (br s, 1H), 8.38 (br s, 1H), 7.96 (d, 1H), 7.91 (d, 1H), 7.68 (d, 1H), 7.58 (d, 1H), 7.46 (t, 1H), 7.39-7.35 (m, 3H), 7.07 (d, 2H), 6.67 (dd, 1H), 6.34 (m, 1H), 6.28 (d, 1H), 3.31 (br s, 2H), 3.17 (br s, 8H), 2.18 (m, 2H), 1.98 (br s, 2H), 1.42 (t, 2H), 0.94 (s, 6H).

## Example 83

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 83A

3-Nitro-4-[1-(2,2,2-trifluoro-ethyl)-piperidin-4-ylamino]-benzenesulfonamide

The title compound was prepared by substituting 1-(2,2,2-trifluoroethyl)piperidin-4-amine hydrochloride for (tetrahydropyran-4-yl)methylamine in EXAMPLE 6A.

## Example 83B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 82A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (br s, 1H), 8.56 (d, 1H), 8.24 (d, 1H), 8.04 (d, 1H), 7.81 (dd, 1H), 7.52 (dd, 2H), 7.48 (d, 1H), 7.35 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38

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(m, 1H), 6.20 (d, 1H), 3.68 (m, 1H), 3.22 (q, 2H), 3.07 (br s, 4H), 2.90 (m, 2H), 2.75 (br s, 2H), 2.29-2.12 (m, 8H), 1.97-1.86 (m, 4H), 1.63 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 84

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 84A

1-(tetrahydro-2H-pyran-4-yl)piperidin-4-ol

Piperidin-4-ol (7.8 g) and dihydro-2H-pyran-4(3H)-one (5.0 g) were dissolved in titanium(IV) isopropoxide (30 mL) and the reaction was stirred at room temperature overnight. Methanol (40 mL) was added and the reaction was cooled to 0° C. Then NaBH<sub>4</sub> (3.8 g) was added in portions over one hour. After 2 hours 1N aqueous NaOH was added, followed by ethyl acetate addition. After filtration through celite the layers were separated, the aqueous layer extracted with ethyl acetate, and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The crude was purified by column chromatography using dichloromethane having 5-10% 7N NH<sub>3</sub> in methanol.

## Example 84B

5-bromo-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 84A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 84C

5-cyano-6-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 84B for EXAMPLE 36B in EXAMPLE 36C.

## Example 84D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]oxy}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 84C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.60 (d, 1H), 8.37 (d, 1H), 7.90 (d, 1H), 7.60 (d, 1H), 7.42 (dd, 1H), 7.35 (d, 2H), 7.25 (d, 1H), 7.04 (d, 2H), 6.63 (dd, 1H), 6.28 (m, 1H), 6.24 (d, 1H), 5.30 (br s, 1H), 4.50 (d, 2H), 3.95 (dd, 2H), 3.30 (m, 5H), 3.02 (br s, 4H), 2.95 (br s, 2H), 2.24 (br s,

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4H), 2.17 (br m, 4H), 1.96 (s, 2H), 1.90 (br m, 4H), 1.60 (br m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 85

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 85A

5-isopropyl-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 36B (0.176 g), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.041 g), and palladium(II) acetate (0.011 g) were combined in a 10 mL oven-dried flask. Tetrahydrofuran (1 mL) was added and the mixture was flushed with nitrogen and stirred at ambient temperature for 5 minutes. 2-Propylzinc bromide solution (0.5 M in tetrahydrofuran) (1.5 mL) was added and stirring was continued under nitrogen overnight. Additional 2-2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.041 g) and palladium(II) acetate (0.011 g) were added. The mixture was flushed with nitrogen and stirred at ambient temperature for 5 minutes. 2-Propylzinc bromide solution (0.5 M in tetrahydrofuran) (1.5 mL) was added and stirring was continued under nitrogen for 2.5 days. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated, and chromatographed on silica gel with 0 to 3% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent. The obtained material was chromatographed on silica gel a second time with 10-40% ethyl acetate in CH<sub>2</sub>Cl<sub>2</sub> as the eluent, triturated with diethyl ether and dried under vacuum at 45° C. to give the product.

## Example 85B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([5-isopropyl-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 85A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 8.49 (m, 1H), 8.04 (d, 1H), 7.90 (m, 1H), 7.57 (m, 1H), 7.52 (t, 1H), 7.48 (dd, 1H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.17 (s, 1H), 4.19 (m, 2H), 3.88 (m, 2H), 3.30 (m, 2H), 3.05 (m, 5H), 2.77 (s, 2H), 2.21 (s, 4H), 2.14 (s, 2H), 2.03 (m, 1H), 1.95 (s, 2H), 1.64 (m, 2H), 1.34 (m, 4H), 1.12 (d, 6H), 0.92 (s, 6H).

## Example 86

N-([3-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 86A

3-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 3,4-difluorobenzenesulfonamide for 4-chloro-3-nitrobenzene-

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sulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 86B

3-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 86A for EXAMPLE 52B in EXAMPLE 52C.

## Example 86C

N-([3-chloro-5-fluoro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 86B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.72 (s, 1H), 11.20 (s, 1H), 8.08 (d, 1H), 7.61 (m, 2H), 7.50 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.42 (dd, 1H), 6.16 (d, 1H), 6.09 (m, 1H), 3.81 (dd, 2H), 3.25 (m, 4H), 3.07 (m, 4H), 2.76 (s, 2H), 2.18 (m, 6H), 1.95 (s, 2H), 1.72 (m, 1H), 1.53 (d, 2H), 1.38 (t, 2H), 1.16 (m, 2H), 0.92 (s, 6H).

## Example 87

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-([3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl]sulfonyl)benzamide

## Example 87A

methyl 2-(1H-indol-5-yloxy)-4-fluorobenzoate

The title compound was prepared by substituting 5-hydroxyindole for EXAMPLE 3G in EXAMPLE 3H.

## Example 87B

methyl 2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 87A for EXAMPLE 3H in EXAMPLE 3I.

## Example 87C

2-(1H-indol-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 87B for EXAMPLE 3I in EXAMPLE 3J.

## Example 87D

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-([3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl]sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 1E in EXAMPLE 1G,



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except here the crude was purified by preparative HPLC using a 250×50 mm C18 column and eluting with 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.40 (br s, 1H), 11.17 (s, 1H), 9.50 (v br s, 1H), 8.61 (t, 1H), 8.57 (d, 1H), 7.77 (dd, 1H), 7.70 (br s, 1H), 7.50 (m, 5H), 7.36 (m, 5H), 7.10 (s, 1H), 7.08 (d, 1H), 6.83 (dd, 1H), 6.69 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.30 (br s, 1H), 3.84 (dd, 2H), 3.70 (br s, 1H), 3.30 (m, 6H), 3.20, 2.95, 2.80 (all br s, total 6H), 1.86 (m, 1H), 1.60 (m, 2H), 1.25 (m, 2H).

## Example 88

4-{4-[(4'-chloro-1,1'-biphenyl-2-yl)methyl]piperazin-1-yl}-2-(1H-indol-5-yloxy)-N-({4-[(3-morpholin-4-ylpropyl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 1E and EXAMPLE 2A for EXAMPLE 1F in EXAMPLE 1G, except here the crude was purified by preparative HPLC using a 250×50 mm C18 column and eluting with 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.40 (br s, 1H), 11.19 (s, 1H), 9.60 (v br s, 1H), 8.69 (t, 1H), 8.60 (d, 1H), 7.83 (dd, 1H), 7.65 (br s, 1H), 7.50 (m, 5H), 7.38 (m, 5H), 7.12 (m, 2H), 6.83 (dd, 1H), 6.69 (dd, 1H), 6.39 (m, 1H), 6.20 (d, 1H), 4.38 (br s, 1H), 4.00 (m, 2H), 3.80 (br s, 1H), 3.40 (m, 4H), 3.30-2.80 (envelope, 10H), 3.20 (m, 4H), 1.96 (m, 2H).

## Example 89

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}phenyl)sulfonylbenzamide

This EXAMPLE was prepared by substituting EXAMPLE 87C for EXAMPLE 1E and EXAMPLE 3M for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.15 (s, 1H), 8.56 (d, 1H), 8.20 (d, 1H), 7.84 (dd, 1H), 7.52 (d, 1H), 7.39-7.31 (m, 4H), 7.12 (d, 2H), 7.04 (d, 2H), 6.84 (dd, 1H), 6.65 (dd, 1H), 6.38 (t, 1H), 6.14 (d, 1H), 3.94 (m, 2H), 3.84 (m, 1H), 3.02 (m, 8H), 2.79 (m, 3H), 2.72 (s, 2H), 2.20-2.02 (m, 8H), 1.85 (m, 6H), 1.60 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 90

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(1-methylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 1E and EXAMPLE 4A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.08 (s, 1H), 8.51 (d, 1H), 8.13 (d, 1H), 7.78 (dd, 1H), 7.52 (d, 1H), 7.37-7.31 (m, 4H), 7.06-7.00 (m, 4H), 6.79 (dd, 1H), 6.59 (dd, 1H), 6.35 (t, 1H), 6.14 (d, 1H), 3.73 (m, 1H), 3.05-2.95 (m, 6H), 2.71 (s, 2H), 2.60 (m, 2H), 2.48 (s, 3H), 2.16 (m, 6H), 2.01 (m, 2H), 1.95 (s, 2H), 1.70 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

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## Example 91

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(4-methylpiperazin-1-yl)amino]-3-nitrophenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 6A for EXAMPLE 11B and EXAMPLE 87C for EXAMPLE 3J in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.14 (s, 1H), 9.18 (s, 1H), 8.53 (d, 1H), 7.84 (dd, 1H), 7.56 (d, 1H), 7.51 (d, 1H), 7.39 (m, 2H), 7.33 (d, 2H), 7.12 (d, 1H), 7.03 (d, 2H), 6.84 (dd, 1H), 6.62 (dd, 1H), 6.38 (m, 1H), 6.13 (d, 1H), 3.00 (m, 4H), 2.90 (m, 4H), 2.71 (s, 2H), 2.33 (s, 3H), 2.15 (m, 6H), 1.94 (s, 2H), 1.37 (t, 2H), 0.92 (s, 6H).

## Example 92

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-(1,4-dioxan-2-ylmethoxy)-3-nitrophenyl}sulfonyl)-2-(1H-indol-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 87C and EXAMPLE 12A in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.16 (s, 2H), 8.39 (d, 1H), 8.06 (dd, 1H), 7.51 (d, 1H), 7.38-7.43 (m, 3H), 7.34 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.85 (dd, 1H), 6.64 (dd, 1H), 6.39 (s, 1H), 6.15 (d, 1H), 4.20-4.28 (m, 2H), 3.85-3.91 (m, 1H), 3.82 (dd, 1H), 3.74-3.78 (m, 1H), 3.59-3.69 (m, 2H), 3.40-3.51 (m, 2H), 3.05 (s, 4H), 2.78 (s, 2H), 2.23 (s, 4H), 2.14 (s, 2H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 93

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(2-methoxyethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 3J and EXAMPLE 16A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.17 (s, 1H), 8.18 (d, 1H), 7.92 (dd, 1H), 7.49 (d, 1H), 7.40 (m, 2H), 7.33 (d, 2H), 7.26 (m, 1H), 7.17 (d, 1H), 7.04 (m, 3H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.40 (s, 1H), 6.14 (d, 1H), 3.51 (m, 4H), 3.28 (s, 3H), 3.03 (s, 4H), 2.74 (s, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 94

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-indol-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 87C for EXAMPLE 3J and EXAMPLE 17A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.20 (s, 1H), 8.19 (d, 1H), 7.90 (dd, 1H), 7.53 (d, 1H), 7.40 (m, 4H), 7.33 (t, 1H), 7.17 (d, 1H), 7.07 (m, 3H), 6.86 (dd, 1H), 6.70 (dd, 1H), 6.41 (s, 1H), 6.21 (d, 1H), 3.84 (dd, 2H), 3.59 (m, 2H), 3.25 (m, 6H), 3.00 (m,

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2H), 2.74 (s, 2H), 2.54 (m, 2H), 2.18 (s, 2H), 2.01 (s, 2H), 1.83 (m, 1H), 1.54 (m, 2H), 1.45 (t, 2H), 1.23 (m, 2H), 0.94 (s, 6H).

**Example 95**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 95A**

1-(1,3-difluoropropan-2-yl)piperidin-4-amine

Tert-butyl piperidin-4-ylcarbamate (0.212 g), 1,3-difluoropropan-2-one (0.149 g) and sodium triacetoxyborohydride (0.337 g) were stirred together in dichloroethane at room temperature. After stirring overnight the reaction was quenched with water (10 mL) and extracted into dichloromethane (2x20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was treated with hydrogen chloride (4.0M in dioxane, 1.323 ml) for 1 hour to give the title compound as the HCl salt after concentration.

**Example 95B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 95A (0.057 g) and EXAMPLE 53A (0.162 g) were suspended in dioxane (3 mL) and heated to 105° C. overnight. The reaction was concentrated, loaded onto silica gel (GraceResolve 12 g) and eluted with a gradient of 0.5% to 4% methanol/dichloromethane. The product containing fractions were concentrated and loaded onto C18 (SF25-75 g analogix column) and eluted using a gradient of 30% to 60% acetonitrile/water. The product was partitioned between dichloromethane (20 mL) and saturated aqueous NaHCO<sub>3</sub> solution (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.10 (s, 1H), 8.88 (d, 2H), 8.45 (d, 1H), 8.20 (s, 1H), 8.18-8.09 (m, 1H), 7.95 (d, 1H), 7.68 (d, 1H), 7.44 (s, 1H), 7.23-7.19 (m, 1H), 6.91 (d, 3H), 6.53 (d, 2H), 5.98 (d, 1H), 4.64 (dd, 4H), 3.68-3.50 (m, 1H), 3.01 (d, 6H), 2.72 (d, 4H), 2.19 (s, 11H), 1.69 (s, 2H), 1.41 (s, 2H), 0.94 (s, 6H).

**Example 96**

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 96A**

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

**280****Example 96B**

N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 96A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 8.03 (d, 1H), 7.56 (d, 1H), 7.50 (m, 2H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.22 (s, 1H), 4.50 (d, 2H), 3.78 (m, 2H), 3.60 (m, 2H), 3.12 (v br s, 4H), 2.93 (v br s, 2H), 2.38 (v br s, 4H), 2.17 (br m, 2H), 1.96 (s, 2H), 1.86 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

**Example 97**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(1-(2,2-difluoroethyl)piperidin-4-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 97A**

tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 4-aminopiperidine-1-carboxylate for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

**Example 97B**

3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide

Tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperidine-1-carboxylate was dissolved in dichloromethane (3 mL) and treated with 1N HCl in ether (4 mL). The reaction was stirred overnight then concentrated to give the title compound.

**Example 97C**

4-(1-(2,2-difluoroethyl)piperidin-4-ylamino)-3-nitrobenzenesulfonamide

3-nitro-4-(piperidin-4-ylamino)benzenesulfonamide hydrochloride (0.100 g), 1,1-difluoro-2-iodoethane (0.063 mL) and diisopropylamine (0.156 mL) were stirred together in N,N-dimethylformamide (3 mL) and heated to 85° C. The reaction was diluted with dichloromethane (50 mL) and washed with water (50 mL), brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel (GraceResolve 12 g) and eluted using a gradient of 0.5% methanol/dichloromethane to 3% methanol/dichloromethane over 30 minutes to give the title compound.

**Example 97D**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-(1-(2,2-difluoroethyl)piperidin-4-yl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 97B for EXAMPLE 1F and EXAMPLE 3J for

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EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.54-11.27 (m, 1H), 8.55 (d, 1H), 8.24 (d, 1H), 8.03 (d, 1H), 7.81 (d, 1H), 7.50 (dd, 3H), 7.34 (d, 2H), 7.13 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.38 (dd, 1H), 6.15 (dt, 2H), 3.64 (s, 1H), 3.07 (s, 4H), 2.79 (ddd, 6H), 2.41 (t, 2H), 2.17 (d, 6H), 1.92 (d, 4H), 1.61 (d, 2H), 1.38 (s, 2H), 0.92 (s, 6H).

## Example 98

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiiperidin-4-amine with 4-amino-1-cyclopropylpiperidine. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.54 (d, 1H), 8.22 (d, 1H), 8.02 (d, 1H), 7.80 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.11 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.69 (m, 1H), 3.06 (m, 4H), 2.92 (m, 2H), 2.74 (s, 2H), 2.23 (m, 7H), 1.93 (m, 5H), 1.77 (m, 1H), 1.55 (m, 3H), 1.38 (t, 2H), 0.92 (s, 6H), 0.43 (m, 4H).

## Example 99

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-morpholin-4-yl)cyclohexyl]methyl}amino)-3-nitrophenyl sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiiperidin-4-amine with 1-(4-morpholino)cyclohexanemethylamine. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 9.06 (s, 1H), 8.59 (d, 1H), 8.06 (d, 1H), 7.83 (dd, 1H), 7.57 (d, 1H), 7.50 (m, 2H), 7.34 (m, 3H), 7.19 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.17 (d, 1H), 3.56 (m, 6H), 3.44 (m, 2H), 3.07 (m, 5H), 2.57 (m, 5H), 2.24 (m, 6H), 1.95 (s, 3H), 1.45 (m, 6H), 1.23 (m, 3H), 0.92 (s, 6H).

## Example 100

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{4-(dicyclopropylamino)cyclohexyl}amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

## Example 100A

Trans-tert-butyl-4-(dicyclopropylamino)cyclohexyl-carbamate

A suspension of trans-tert-butyl-4-aminocyclohexylcarbamate (1 g), molecular sieves 3A (1 g), acetic acid (2.67 ml), (1-ethoxycyclopropoxy)trimethylsilane (3.74 ml) and sodium cyanoborohydride (0.880 g) in dry methanol (10 ml) was heated at reflux for 3 hours. The insolubles were filtered off, the resulting solution was basified with aqueous NaOH (6 M) to pH 14, and extracted with ether. The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography (silica gel 80 g, 30-100% acetone/hexanes) to provide the title compound.

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## Example 100B

(trans)-N<sup>1</sup>,N<sup>1</sup>-dicyclopropylcyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 100A for EXAMPLE 39A in EXAMPLE 39B.

## Example 100C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{4-(dicyclopropylamino)cyclohexyl}amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

A suspension of EXAMPLE 53A (0.14 g), EXAMPLE 100B (0.112 g) and N,N-diisopropylethylamine (0.310 mL) in dioxane (10 mL) was stirred for 3 days at 100° C. The product was concentrated and purified by RP HPLC(C8, 30%-100% CH<sub>3</sub>CN/water/0.1% trifluoroacetic acid). <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.28 (d, 1H), 8.41-8.45 (m, 2H), 8.37 (d, 1H), 8.12 (d, 1H), 7.67 (d, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.01 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48-6.51 (m, 1H), 3.43 (ddd, 1H), 3.03-3.09 (m, 4H), 2.72-2.79 (m, 3H), 2.22-2.28 (m, 2H), 2.11-2.16 (m, 4H), 2.10 (s, 2H), 2.00-2.05 (m, 2H), 1.97 (s, 2H), 1.89 (s, 1H), 1.86 (s, 3H), 1.62-1.71 (m, 2H), 1.39 (t, 2H), 1.19-1.29 (m, 2H), 0.93 (s, 6H), 0.48 (d, 8H).

## Example 101

4-(4-{[2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 101A

## Ethyl

2-hydroxy-6,6-dimethylcyclohex-1-enecarboxylate

Into a 500 mL flame dried round-bottomed flask was added copper(I) iodide (18 g) in ether (200 mL) to give a suspension. After cooling to -5° C., methyl lithium (120 mL, 1.6M in ether) was added dropwise. After stirring at -5° C. for 1 hour, 3-methylcyclohex-2-enone (5.15 mL) in 15 mL ether was added dropwise, and the mixture was stirred at -5° C. for 1 hour. After cooling to -78° C., hexamethylphosphoramide (60 mL) was added dropwise. Ethyl carbonocyanidate (23.74 mL) was added. After stirring at -78° C. for 20 minutes, the mixture was warmed up to room temperature, and stirred for 1 hour. The mixture was poured into cold water, and the layers were separated. The aqueous layer was extracted with ether (3×20 mL). The combined organic layers were washed with saturated aqueous NH<sub>4</sub>Cl (3×20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and dried under vacuum. The crude product was added to a silica gel column and purified by eluting with 0-10% ethyl acetate in hexane.

## Example 101B

Ethyl 6,6-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

Into a 500 mL round-bottomed flask was added hexane-washed sodium hydride (0.5 g) in dichloromethane (100 mL)

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to give a suspension. After cooling to  $-5^{\circ}\text{C}$ ., EXAMPLE 101A (2.0 g) was added. After stirring at  $-5^{\circ}\text{C}$ . for 30 minutes, the mixture was cooled to  $-78^{\circ}\text{C}$ . Trifluoromethane-sulfonic anhydride (2.2 mL) was added. The mixture was warmed to room temperature and stirred overnight. Water was added slowly to the mixture, the aqueous layer was then extracted by dichloromethane (2x20 mL). The combined organic layers were washed with saturated  $\text{NH}_4\text{Cl}$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated.

**Example 101C**

ethyl 2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enecarboxylate

Into a 25 mL microwave tube was added EXAMPLE 101B (2.9 g), 4-chlorophenylboronic acid (2.2 g), and tetrakis(triphenylphosphine)palladium (0.05 g) in 1,2-dimethoxyethane/methanol (2:1, 10 mL) to give a solution. Cesium fluoride (4 g) was then added. The reaction mixture was stirred at  $150^{\circ}\text{C}$ . under (100 W) in a Biotage Initiator microwave reactor for 30 minutes. After removing the solvents, water was added, and the mixture was extracted with ethyl acetate (2x). The combined organic layers were dried by  $\text{MgSO}_4$ . After filtering, the crude product was purified by reverse phase chromatography eluting with 50-100% acetonitrile/water with 0.1% trifluoroacetic acid.

**Example 101 D**

(2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl) methanol

In a 100 mL round-bottomed flask was placed lithium aluminum hydride (1 g) in ether (20 mL) to give a suspension. EXAMPLE 101C (1 g) dissolved in ether (5 mL) was added slowly by syringe. The mixture was stirred at room temperature overnight. After cooling to  $0^{\circ}\text{C}$ ., the reaction was quenched by water. Ether (2x10 mL) was used to extract the product. The crude product was purified by flash chromatography on silica by eluting with 0-15% ethyl acetate in hexane.

**Example 101E**

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

To a  $0^{\circ}\text{C}$ . solution of EXAMPLE 101D (0.43 g) in dichloromethane (5 mL) was added triethylamine (1 mL). Methanesulfonyl chloride (0.134 mL) was then added slowly. After 5 minutes, EXAMPLE 15F (0.61 g) was added. The mixture was stirred at room temperature overnight. The crude product was purified by flash chromatography on silica with 0 to 25% ethyl acetate in hexanes to provide the title compound.

**Example 101F**

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

In a 5 mL microwave tube was added lithium hydroxide hydrate (15 mg) and EXAMPLE 101E (45 mg) in dioxane/water (2:1) (2 mL) to give a suspension. The mixture was heated to  $130^{\circ}\text{C}$ . in a Biotage Initiator microwave reactor for 20 minutes. After cooling and neutralization by HCl, the

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crude product was added to a Prep HPLC column and was eluted with 20-80% acetonitrile/water with 0.1% trifluoroacetic acid.

**Example 101G**

4-(4-([2-(4-chlorophenyl)-6,6-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 101F for EXAMPLE 3J and EXAMPLE 1F for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.68 (s, 1H), 11.47 (s, 1H), 8.58 (m, 2H), 8.03 (m, 1H), 7.79 (m, 1H), 7.51 (m, 3H), 7.31 (d, 2H), 7.10 (m, 1H), 7.02 (d, 2H), 6.65 (m, 1H), 6.39 (m, 1H), 6.15 (m, 1H), 3.85 (m, 2H), 3.27 (m, 4H), 2.97 (m, 4H), 2.76 (s, 2H), 2.14 (m, 6H), 1.70 (m, 2H), 1.61 (m, 2H), 1.44 (m, 2H), 1.26 (m, 3H), 1.16 (m, 6H)

**Example 102**

N-([5-bromo-6-((4-ethylmorpholin-3-yl)methoxy)pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 102A**

(4-ethylmorpholin-3-yl)methanol

Morpholin-3-ylmethanol (500 mg) and iodoethane (666 mg) in N,N-dimethylformamide was treated with  $\text{K}_2\text{CO}_3$  (1.1 g) overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to provide the title compound.

**Example 102B**

5-bromo-6-((4-ethylmorpholin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing 4-fluoro-3-nitrobenzenesulfonamide and (1,4-dioxan-2-yl)methanol with 5-bromo-6-fluoropyridine-3-sulfonamide and EXAMPLE 102A, respectively.

**Example 102C**

N-([5-bromo-6-((4-ethylmorpholin-3-yl)methoxy)pyridin-3-yl]sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 102B in place of EXAMPLE 11B.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.62 (s, 1H), 8.51 (s, 1H), 8.30 (s, 1H), 8.00 (d, 1H), 7.55 (d, 1H), 7.45-7.50 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.37 (s, 1H), 6.21 (d, 1H), 4.58 (dd, 1H), 4.39-4.50 (m, 1H), 3.78-3.90 (m, 1H), 3.67-3.77 (m, 1H), 3.50-3.65 (m,



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2H), 3.08 (s, 4H), 2.59-3.00 (m, 4H), 2.20-2.39 (m, 2H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 0.99-1.11 (m, 3H), 0.93 (s, 6H)

## Example 103

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 103A

4-((4-ethylmorpholin-3-yl)methoxy)-3-nitrobenzene-sulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with EXAMPLE 102A.

## Example 103B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-ethylmorpholin-3-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 103A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.33 (s, 1H), 7.99-8.06 (m, 2H), 7.47-7.57 (m, 3H), 7.45 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.42 (dd, 1H), 4.23 (dd, 1H), 3.81 (d, 1H), 3.69 (d, 1H), 3.49-3.63 (m, 2H), 3.08 (s, 4H), 2.92 (s, 1H), 2.81 (s, 4H), 2.54 (s, 1H), 2.25 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.39 (t, 2H), 1.00 (t, 3H), 0.92 (s, 6H)

## Example 104

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(4-tetrahydro-2H-pyran-4-yl)morpholin-3-yl]methoxy}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 78 (20 mg) and dihydro-2H-pyran-4(3H)-one (10 mg) in dichloroethane (2 mL) was treated with NaCNBH<sub>3</sub> (9.74 mg) overnight. Additional dihydro-2H-pyran-4(3H)-one (20 mg) and titanium (IV) isopropoxide (0.05 mL) were added. The resulting mixture was stirred at room temperature overnight and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 35-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.35 (s, 1H), 8.04 (s, 2H), 7.44-7.58 (m, 4H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 4.44 (s, 1H), 4.28 (s, 1H), 3.85 (d, 2H), 3.71 (d, 1H), 3.61 (s, 3H), 3.20-3.29 (m, 2H), 3.08 (s, 5H), 2.54-2.96 (m, 5H),

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2.06-2.42 (m, 5H), 1.96 (s, 2H), 1.77 (d, 1H), 1.53-1.66 (m, 1H), 1.29-1.51 (m, 4H), 0.92 (s, 6H)

## Example 105

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-yl]piperidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 105A

(S)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)piperidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl piperidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 105B

(S)-1-(tetrahydro-2H-pyran-4-yl)piperidin-3-amine

The title compound was prepared by substituting EXAMPLE 105A for EXAMPLE 1A in EXAMPLE 1B.

## Example 105C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-yl]piperidin-3-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 105B for 1-acetyl piperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 8.68 (br s, 1H), 8.54 (br s, 1H), 8.02 (d, 1H), 7.77 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 3.98 (m, 2H), 3.90 (m, 2H), 3.52 (m, 2H), 3.09 (s, 2H), 3.05 (m, 4H), 2.77 (m, 2H), 2.60 (m, 2H), 2.16 (m, 6H), 1.95 (m, 2H), 1.65 (m, 5H), 1.50 (m, 3H), 1.38 (m, 2H), 0.94 (s, 6H).

## Example 106

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tetrahydro-2H-pyran-4-yl)methyl]amino}pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 106 A

5-Bromo-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting (tetrahydro-2H-pyran-4-yl)methanamine for EXAMPLE 3L in EXAMPLE 61A.

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Example 106B

5-cyano-6-((tetrahydro-2H-pyran-4-yl)methylamino)  
pyridine-3-sulfonamide

The title compound was prepared by substituting  
EXAMPLE 106A for EXAMPLE 36B in EXAMPLE 36C.

Example 106C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-  
en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-6-[(tet-  
rahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-  
yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)  
benzamide

The title compound was prepared by substituting  
EXAMPLE 106B for EXAMPLE 11B in EXAMPLE 11D.  
<sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.62 (s, 1H),  
8.55 (s, 1H), 8.14 (s, 1H), 8.01 (d, 1H), 7.87 (s, 1H), 7.56 (d,  
1H), 7.48 (d, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (m, 1H),  
6.37 (s, 1H), 6.19 (d, 1H), 3.81 (dd, 2H), 3.25 (m, 4H), 3.04 (s,  
4H), 2.74 (s, 2H), 2.17 (m, 6H), 1.95 (s, 2H), 1.87 (m, 1H),  
1.53 (m, 2H), 1.37 (t, 2H), 1.18 (m, 2H), 0.91 (s, 6H).

Example 107

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclo-  
hex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-  
dioxidothiomorpholin-4-yl)amino]-3-  
nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

Example 107A

3-nitro-4-(4-aminothiomorpholine-1,1-dioxide)ben-  
zenesulfonamide

The title compound was prepared by substituting 4-ami-  
nothiomorpholine-1,1-dioxide for (tetrahydropyran-4-yl)  
methylamine in EXAMPLE 1F.

Example 107B

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclo-  
hex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,1-  
dioxidothiomorpholin-4-yl)amino]-3-  
nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 107A for EXAMPLE 11B in EXAMPLE 11D.  
<sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H),  
9.58 (s, 1H), 8.50 (s, 1H), 8.02 (d, 1H), 7.78 (m, 2H), 7.50 (m,  
3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.38 (s, 1H),  
6.19 (d, 1H), 3.48 (m, 4H), 3.23 (m, 4H), 3.05 (s, 4H), 2.73 (d,  
2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

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Example 108

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]  
amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlo-  
rophenyl)-4,4-dimethylcyclohex-1-en-1-yl]  
methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

Example 108A

4-((4-aminotetrahydro-2H-pyran-4-yl)methylamino)-  
3-nitrobenzenesulfonamide

The title compound was prepared by substituting 4-(ami-  
nomethyl)tetrahydro-2H-pyran-4-amine for (tetrahydro-2H-  
pyran-4-yl)methanamine in EXAMPLE 1F.

Example 108B

N-[(4-{[(4-aminotetrahydro-2H-pyran-4-yl)methyl]  
amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlo-  
rophenyl)-4,4-dimethylcyclohex-1-en-1-yl]  
methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-  
5-yloxy)benzamide

The title compound was prepared by substituting  
EXAMPLE 108A for EXAMPLE 11B in EXAMPLE 11D.  
<sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.55 (s, 1H),  
8.45 (s, 2H), 7.95 (d, 1H), 7.75-7.77 (m, 1H), 7.57 (d, 2H),  
7.44 (s, 1H), 7.34 (d, 2H), 7.09 (d, J=8.85 Hz, 1H), 7.05 (d,  
2H), 6.69 (dd, 1H), 6.33 (d, 1H), 6.22 (d, 1H), 3.59-3.71 (m,  
6H), 3.01 (s, 4H), 2.73 (s, 2H), 2.15-2.19 (m, 6H), 1.95 (s,  
2H), 1.71-1.74 (m, 2H), 1.59-1.61 (m, 1H), 1.38 (t, 2H), 0.93  
(s, 6H).

Example 109

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclo-  
hex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-  
6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-  
yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)  
benzamide

Example 109A

Trans-5-bromo-6-(4-morpholinocyclohexyloxy)pyri-  
dine-3-sulfonamide

The title compound was prepared by substituting  
EXAMPLE 9B for EXAMPLE 3L in EXAMPLE 61A.

Example 109B

Trans-5-cyano-6-(4-morpholinocyclohexylamino)  
pyridine-3-sulfonamide

The title compound was prepared by substituting  
EXAMPLE 109A for EXAMPLE 36B in EXAMPLE 36C.

Example 109C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclo-  
hex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-cyano-  
6-[(4-morpholin-4-ylcyclohexyl)amino]pyridin-3-  
yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)  
benzamide

The title compound was prepared by substituting  
EXAMPLE 109B for EXAMPLE 11B in EXAMPLE 11D.

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<sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.56 (d, 1H), 8.13 (s, 1H), 8.00 (d, 1H), 7.55 (d, 1H), 7.47 (m, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.36 (d, 1H), 6.19 (d, 1H), 4.00 (m, 1H), 3.65 (m, 4H), 3.28 (m, 4H), 3.03 (m, 4H), 2.73 (m, 4H), 2.16 (m, 6H), 1.90 (m, 6H), 1.40 (m, 6H), 0.93 (s, 6H).

## Example 110

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 52B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.23 (s, 1H), 8.08 (d, 1H), 7.91 (d, 1H), 7.74 (dd, 1H), 7.60 (d, 1H), 7.52 (m, 2H), 7.34 (m, 2H), 7.16 (s, 1H), 7.04 (m, 2H), 6.83 (d, 1H), 6.68 (dd, 1H), 6.43 (dd, 1H), 6.16 (d, 1H), 3.83 (dd, 2H), 3.23 (m, 2H), 3.12 (t, 2H), 3.06 (m, 4H), 2.73 (m, 2H), 2.15 (m, 6H), 1.95 (s, 2H), 1.82 (m, 1H), 1.58 (m, 2H), 1.38 (m, 2H), 1.18 (m, 2H), 0.92 (s, 6H).

## Example 111

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 111A

benzyl(1S,3R)-3-(tert-butoxycarbonylamino)cyclopentylcarbamate

(1S,3R)-3-(tert-butoxycarbonylamino)cyclopentanecarboxylic acid (1.03 g), diphenylphosphoryl azide (DPPA, 1.00 mL), triethylamine (0.929 mL), and benzyl alcohol (0.931 mL) were combined in toluene (10 mL) and stirred at 100° C. for 24 hours. The solution was cooled and chromatographed on silica gel using 10% ethyl acetate/hexanes to give the pure product.

## Example 111B

benzyl(1S,3R)-3-aminocyclopentylcarbamate

The title compound was prepared by substituting EXAMPLE 111A for EXAMPLE 1A in EXAMPLE 1B.

## Example 111C

benzyl(1S,3R)-3-morpholinocyclopentylcarbamate

A solution of EXAMPLE 111B (400 mg), 1-bromo-2-(2-bromoethoxy)ethane (0.246 mL), and triethylamine (0.595 mL) in N,N-dimethylformamide (6 mL) was stirred at 70° C. for 24 hours. The solution was cooled and poured into ethyl acetate (200 mL). The solution was extracted with 3× water, washed with brine, concentrated, and chromatographed on silica gel using 10% methanol/ethyl acetate to give the pure product.

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## Example 111D

(1S,3R)-3-morpholinocyclopentanamine

EXAMPLE 111C (300 mg) and ethanol (20 mL) were added to wet 20% Pd(OH)<sub>2</sub>-C (60.0 mg) in a 50 mL pressure bottle and stirred for 8 hours at 30 psi. The mixture was filtered through a nylon membrane and condensed to give the product.

## Example 111E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1S,3R)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 111D for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.45 (d, 1H), 8.28 (dd, 1H), 7.97 (d, 1H), 7.68 (d, 1H), 7.52 (d, 1H), 7.44 (d, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.92 (dd, 1H), 6.85 (dd, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 4.08 (m, 1H), 3.60 (br s, 4H), 3.06 (br s, 4H), 2.73 (br s, 3H), 2.48 (m, 4H), 2.28 (m, 1H), 2.18 (m, 6H), 2.07 (m, 1H), 1.95 (s, 2H), 1.79 (m, 2H), 1.63 (m, 2H), 1.38 (t, 2H), 0.93 (s, 6H).

## Example 112

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 112A

tert-butyl(1R,3S)-3-aminocyclopentylcarbamate

The title compound was prepared by substituting EXAMPLE 111A for EXAMPLE 111C in EXAMPLE 111D.

## Example 112B

tert-butyl(1R,3S)-3-morpholinocyclopentylcarbamate

The title compound was prepared by substituting EXAMPLE 112A for EXAMPLE 111B in EXAMPLE 111C.

## Example 112C

(1R,3S)-3-morpholinocyclopentanamine

The title compound was prepared by substituting EXAMPLE 112B for EXAMPLE 1A in EXAMPLE 1B.

## Example 112D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,3S)-3-morpholin-4-ylcyclopentyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 112C for

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EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (dimethylsulfoxide-d<sub>6</sub>) δ 11.35 (s, 1H), 8.51 (d, 1H), 8.44 (dd, 1H), 8.00 (d, 1H), 7.77 (d, 1H), 7.50 (d, 1H), 7.48 (s, 2H), 7.34 (d, 2H), 7.04 (d, 2H), 7.02 (dd, 1H), 6.67 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.11 (m, 1H), 3.61 (br s, 4H), 3.06 (br s, 4H), 2.73 (br s, 3H), 2.50 (m, 4H), 2.28 (m, 1H), 2.18 (m, 6H), 2.06 (m, 1H), 1.95 (s, 2H), 1.77 (m, 2H), 1.66 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 113

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 113A

tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 113B

tert-butyl 2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 113A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G, with the exception that the product was purified on a silica gel column eluted with 4% methanol in dichloromethane.

## Example 113C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(morpholin-2-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 113B for EXAMPLE 66B in EXAMPLE 66C. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.55 (br s, 1H), 8.51 (s, 1H), 8.00 (d, 1H), 7.80 (d, 1H), 7.52 (d, 1H), 7.49-7.46 (m, 2H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.36 (s, 1H), 6.20 (d, 1H), 4.00 (dd, 1H), 3.91 (m, 1H), 3.70 (t, 1H), 3.60 (m, 1H), 3.58 (m, 1H), 3.32 (m, 1H), 3.16 (d, 1H), 3.05 (m, 4H), 2.98 (td, 1H), 2.86 (t, 1H), 2.73 (s, 2H), 2.20-2.12 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 114

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 114A

3-nitro-4-((tetrahydrofuran-3-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 3-aminomethyl-tetrahydrofuran for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

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## Example 114B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 114A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.42 (bs, 1H), 8.63 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.53-7.48 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.82-3.79 (m, 1H), 3.71 (t, 1H), 3.62 (dd, 1H), 3.50 (dd, 1H), 3.38 (m, 1H), 3.32 (m, 1H), 3.07 (m, 4H), 2.76 (s, 2H), 2.58 (m, 1H), 2.25-2.00 (m, 6H), 1.98 (m, 1H), 1.95 (s, 2H), 1.65 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 115

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 115A

Cis-tert-butyl 1-(3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-ylcarbamate

The title compound was prepared as a racemate of the cis diastereomer by substituting tert-butyl piperidin-4-ylcarbamate for piperidin-4-ol and 3-fluorodihydro-2H-pyran-4(3H)-one (prepared by the method described in US2005/0101628A1) for dihydro-2H-pyran-4(3H)-one in EXAMPLE 84A.

## Example 115B

Cis-1-(3-fluorotetrahydro-2H-pyran-4-yl)piperidin-4-amine

Example 115A (0.29 g) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (9 mL), then 4N HCl in dioxane (4 mL) was added and the reaction stirred at room temperature for 16 hours. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL), then 4N aqueous NaOH (5 mL) was added. After shaking and separating the layers the aqueous layer was saturated with solid NaCl and extracted with more CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration the amine was used with no further purification.

## Example 115C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[cis-3-fluorotetrahydro-2H-pyran-4-yl]piperidin-4-yl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 115B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.54 (d, 1H), 8.43 (br d, 1H), 8.03 (d, 1H), 7.80 (dd, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.11 (d, 1H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.38 (m, 1H), 6.20 (d, 1H), 4.92 (d,



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1H), 3.95 (m, 2H), 3.70 (v br m, 1H), 3.50, 3.40, 3.30 (all m, total 5H), 3.05, 3.00 (both v br m, total 5H), 2.74 (s, 2H), 2.55 (v br m, 1H), 2.18 (br m, 6H), 1.95 (m, 4H), 1.88 (ddd, 1H), 1.63 (v br m, 3H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 116

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)azetidin-3-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 116A

1-(tetrahydro-2H-pyran-4-yl)azetidin-3-amine

Tert-butyl azetidin-3-ylcarbamate (0.46 g), dihydro-2H-pyran-4(3H)-one (0.29 g) and sodium triacetoxymethylborohydride (0.85 g) were stirred together in dichloromethane (5 mL) overnight. The reaction was poured into dichloromethane (50 mL) and saturated aqueous NaHCO<sub>3</sub> solution (25 mL). The organic layer was separated, washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane over 20 minutes gave the Boc-protected intermediate. Treatment with HCl (4.0M in dioxane, 2 mL) and methanol (1 mL) for 1 hour gave the title compound after concentration as the di-HCl salt.

## Example 116B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro-2H-pyran-4-yl)azetidin-3-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A suspension of 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-chloro-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide (0.180 g), 1-(tetrahydro-2H-pyran-4-yl)azetidin-3-amine (0.078 g), and triethylamine (0.159 mL) in dioxane (2 mL) was degassed with nitrogen for 30 seconds then scaled. The reaction was heated to 110° C. After stirring for 16 hours, more triethylamine (10 equivalents total) and dimethylsulfoxide (1 mL) were added and the reaction stirred for an additional 18 hours at 110° C. The reaction was cooled, diluted with water (50 mL) and extracted with dichloromethane (2x150 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 7.5% methanol/dichloromethane (Flow=36 mL/minutes) gave the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.49 (d, 1H), 8.40 (s, 1H), 7.97 (d, 1H), 7.77 (s, 1H), 7.47 (dd, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90-6.78 (m, 1H), 6.65 (d, 1H), 6.35 (s, 1H), 6.21 (s, 1H), 4.47-4.23 (m, 1H), 3.83 (s, 3H), 3.05 (s, 6H), 2.73 (s, 2H), 2.18 (s, 8H), 1.95 (s, 2H), 1.68 (s, 2H), 1.38 (s, 2H), 1.24 (s, 4H), 0.92 (s, 6H).

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Example 117

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro furan-3-yl)azetidin-3-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 117A

1-(tetrahydrofuran-3-yl)azetidin-3-amine

Tert-butyl azetidin-3-ylcarbamate (0.550 g), dihydrofuran-3(2H)-one (0.412 g) and sodium triacetoxymethylborohydride (1.015 g) were stirred together in dichloromethane (5 mL). After stirring overnight, the reaction was poured into saturated aqueous NaHCO<sub>3</sub> solution (25 mL) and extracted with dichloromethane (50 mL). The organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes gave tert-butyl 1-(tetrahydrofuran-3-yl)azetidin-3-ylcarbamate. The resulting material was treated with HCl/dioxane for 1 hour, and then concentrated to give the title compound.

## Example 117B

3-nitro-4-(1-(tetrahydrofuran-3-yl)azetidin-3-ylamino)benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (0.084 g), 1-(tetrahydrofuran-3-yl)azetidin-3-amine (0.090 g) and triethylamine (0.266 mL) in tetrahydrofuran (3 mL) was heated to 60° C. After stirring for 4 hours, the reaction was cooled, the tetrahydrofuran was removed and the residue was partitioned between dichloromethane (200 mL) and water (20 mL). The organic layer was separated, washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated to give the title compound.

## Example 117C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro furan-3-yl)azetidin-3-yl]amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 117B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.39-9.79 (m, 1H), 9.17 (s, 1H), 8.87 (d, 1H), 8.51 (d, 1H), 8.15 (dd, 2H), 7.94 (d, 1H), 7.68 (d, 1H), 7.48-7.42 (m, 1H), 7.23 (d, 2H), 6.91 (d, 2H), 6.69 (d, 1H), 6.54 (dd, 2H), 5.99 (d, 1H), 4.29 (d, 1H), 4.01-3.73 (m, 4H), 3.66 (d, 2H), 3.08 (s, 6H), 2.76 (s, 2H), 2.21 (s, 6H), 2.03-1.83 (m, 3H), 1.64 (s, 2H), 1.42 (d, 2H), 0.93 (s, 6H).

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## Example 118

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-  
({(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]  
methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-  
b]pyridin-5-yloxy)benzamide

## Example 118A

(R)-tert-butyl(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 118B

(R)-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 118A for EXAMPLE 1A in EXAMPLE 1B.

## Example 118C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-  
({(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]  
methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-  
b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 118B for 1-acetyl piperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.57 (s, 1H), 8.59 (br s, 1H), 8.45 (br s, 1H), 8.02 (d, 1H), 7.95 (m, 1H), 7.71 (m, 1H), 7.56 (d, 1H), 7.45 (m, 1H), 7.35 (m, 3H), 7.05 (m, 2H), 6.90 (br s, 1H), 6.64 (d, 1H), 6.33 (m, 1H), 6.22 (m, 1H), 3.90 (m, 2H), 3.44 (m, 2H), 3.27 (m, 4H), 3.02 (m, 5H), 2.73 (m, 3H), 2.59 (m, 2H), 2.19 (m, 6H), 1.95 (m, 2H), 1.85 (m, 2H), 1.64 (m, 1H), 1.50 (m, 2H), 1.39 (m, 2H), 1.23 (m, 1H), 0.94 (s, 6H).

## Example 119

4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 75F and EXAMPLE 37D in place of EXAMPLE 3J and EXAMPLE 11B, respectively. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.39 (s, 1H), 8.08 (d, 1H), 8.04 (d, 1H), 7.41-7.59 (m, 4H), 7.35 (d, 2H), 7.08 (d, 2H), 6.68 (dd, 1H), 6.37-6.43 (m, 1H), 6.20 (s, 1H), 4.38 (d, 2H), 3.73-3.82 (m, 2H), 3.54-3.63 (m, 2H), 3.09 (s, 4H), 2.81 (s, 2H), 2.16-2.39 (m, 5H), 1.94 (s, 2H), 1.79-1.93 (m, 4H), 1.40 (t, 2H), 0.94 (s, 6H).

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## Example 120

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

## Example 120A

## Trans-4-(aminomethyl)cyclohexanol

Tert-butyl((1r,4r)-4-hydroxycyclohexyl)methylcarbamate (1 g) in dichloromethane (10 mL) was treated with trifluoroacetic acid (5 mL) at 0° C. for 10 minutes and at room temperature for 30 minutes. The reaction mixture was concentrated and dried in vacuo to provide the title compound as a trifluoroacetic acid salt.

## Example 120B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((trans-4-hydroxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

A mixture of EXAMPLE 53A (211 mg), EXAMPLE 120A (104 mg) and N-ethyl-N-isopropylpropan-2-amine (0.3 mL) in dimethylsulfoxide (2 mL) was heated at 150° C. in a Biotage Initiator microwave synthesizer for 1.5 hours and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (30 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the title compound. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.61 (t, 1H), 8.53-8.58 (m, 1H), 8.04 (d, 1H), 7.76-7.83 (m, 1H), 7.47-7.56 (m, 3H), 7.34 (d, 2H), 7.07-7.11 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.82-4.99 (m, 1H), 4.50 (d, 1H), 3.26-3.31 (m, 2H), 3.23 (t, 1H), 3.07 (s, 4H), 2.76 (s, 2H), 2.10-2.28 (m, 6H), 2.05 (dd, 1H), 1.95 (s, 2H), 1.84 (t, 2H), 1.52-1.76 (m, 2H), 1.41-1.51 (m, 1H), 1.38 (t, 2H), 0.95-1.25 (m, 4H), 0.92 (s, 6H).

## Example 121

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonyl)benzamide

## Example 121A

## (4-methoxycyclohexyl)methanol

4-Methoxycyclohexanecarboxylic acid (7 g) in tetrahydrofuran (20 mL) was treated with 1 M (in tetrahydrofuran) borane-tetrahydrofuran complex (100 mL) overnight. The mixture was concentrated and the residue was dissolved in methanol (100 mL) and concentrated HCl (10 mL). The resulting mixture was stirred for 1 hour and concentrated. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the title compound.

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## Example 121B

4-((4-methoxycyclohexyl)methoxy)-3-nitrobenzene-sulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with EXAMPLE 121A.

## Example 121C

4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

Separation of the cis and trans mixture of EXAMPLE 121B on a reverse phase HPLC (gradient: 40-55% acetonitrile in 0.1% TFA in water over 25 minutes) provided the title compound.

## Example 121D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-4-((cis-4-methoxycyclohexyl)methoxy)-3-nitrophenylsulfonamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 121C in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.39 (s, 1H), 8.34 (s, 1H), 7.96-8.07 (m, 2H), 7.48-7.56 (m, 3H), 7.31-7.42 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.39 (s, 1H), 3.20 (s, 3H), 3.09 (s, 4H), 2.82 (s, 2H), 2.09-2.34 (m, 6H), 1.96 (s, 2H), 1.78-1.86 (m, 3H), 1.54 (dd, 2H), 1.28-1.46 (m, 6H), 0.92 (s, 6H)

## Example 122

Cis-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(cyclopropylamino)cyclohexyl]amino)-3-nitrophenylsulfonamide

## Example 122A

Cis-tert-butyl-4-(cyclopropylamino)cyclohexylcarbamate

The title compound was prepared by substituting tert-butyl 4-oxocyclohexylcarbamate for 4'-chlorobiphenyl-2-carboxaldehyde and cyclopropylamine for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 122B

cis-N<sup>1</sup>-cyclopropylcyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 122A for EXAMPLE 39A in EXAMPLE 39B.

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## Example 122C

Cis-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(cyclopropylamino)cyclohexyl]amino)-3-nitrophenylsulfonamide

The title compound was prepared by substituting EXAMPLE 122B for EXAMPLE 100B in EXAMPLE 100C. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.28 (d, 1H), 8.59 (d, 1H), 8.44 (d, 1H), 8.37 (dd, 1H), 8.12 (d, 1H), 7.67 (t, 2H), 7.43 (t, 2H), 7.07 (d, 2H), 6.90 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.50 (dd, 1H), 3.56-3.63 (m, 1H), 3.02-3.08 (m, 4H), 2.77 (s, 3H), 2.26 (t, 2H), 2.10-2.16 (m, 4H), 2.06 (ddd, 1H), 1.97 (s, 2H), 1.74-1.82 (m, 2H), 1.61-1.71 (m, 5H), 1.39 (t, 2H), 0.93 (s, 6H), 0.39-0.44 (m, 4H).

## Example 123

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino)phenyl)sulfonamide

## Example 123A

Trans-tert-butyl-4-(tetrahydro-2H-pyran-4-ylamino)cyclohexylcarbamate

The title compound was prepared by substituting trans-tert-butyl-4-aminocyclohexylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 123B

trans-N<sup>1</sup>-(tetrahydro-2H-pyran-4-yl)cyclohexane-1,4-diamine bis(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 123A for EXAMPLE 39A in EXAMPLE 39B.

## Example 123C

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]amino)phenyl)sulfonamide

The title compound was prepared by substituting EXAMPLE 123B for EXAMPLE 100B in EXAMPLE 100C. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.28 (d, 1H), 8.48 (d, 1H), 8.38 (dd, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 7.67-7.69 (m, 2H), 7.44 (d, 2H), 7.08 (d, 2H), 6.91 (d, 1H), 6.78 (dd, 1H), 6.59 (d, 1H), 6.48 (dd, 1H), 4.01 (d, 2H), 3.44-3.49 (m, 1H), 3.37-3.43 (m, 2H), 3.01-3.09 (m, 5H), 2.85 (t, 1H), 2.78 (s, 2H), 2.27 (t, 2H), 2.13-2.18 (m, 4H), 2.05 (t, 4H), 1.97 (s, 2H), 1.93 (d, 2H), 1.52-1.60 (m, 2H), 1.44-1.50 (m, 2H), 1.39 (t, 2H), 1.25-1.34 (m, 2H), 0.94 (s, 6H).

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## Example 124

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 124A

## Trans-4-morpholinocyclohexanol

Trans-4-Aminocyclohexanol (0.5 g), 1-bromo-2-(2-bromoethoxy)ethane (1.07 g) and triethylamine (2.42 mL) were dissolved in anhydrous acetonitrile (20 mL). The reaction mixture was heated at 60° C. overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 7%-10% methanol in dichloromethane to give the title compound.

## Example 124B

Trans-5-bromo-6-(4-morpholinocyclohexyloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 124A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 124C

Trans-N-({5-bromo-6-[(4-morpholin-4-ylcyclohexyl)oxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 124B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 3.07 (m, 4H), 2.89 (m, 1H), 2.71 (m, 2H), 2.16 (m, 6H), 1.96 (s, 3H), 1.80 (m, 4H), 1.38 (t, 2H), 1.27 (m, 2H), 0.92 (s, 6H).

## Example 125

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 125A

4-(((trans)-4-methoxycyclohexyl)methoxy)-3-nitrobenzenesulfonamide

Separation of the cis and trans mixture of EXAMPLE 121B on a reverse phase HPLC provided the title compound.

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## Example 125B

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxycyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 125A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.34 (s, 1H), 7.96-8.09 (m, 2H), 7.51 (dd, 3H), 7.32-7.39 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.24 (s, 3H), 3.00-3.15 (m, 5H), 2.83 (s, 2H), 2.09-2.36 (m, 6H), 2.03 (d, 2H), 1.96 (s, 2H), 1.77-1.86 (m, 2H), 1.73 (s, 1H), 1.39 (t, 2H), 1.02-1.17 (m, 4H), 0.92 (s, 6H)

## Example 126

tert-butyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl]-2-nitrophenoxy[methyl]-4-fluoropiperidine-1-carboxylate

## Example 126A

tert-butyl  
4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (5 mL) was treated with 1.0 N LiAlH<sub>4</sub> in THF (2.54 mL) at 0° C. The reaction mixture was stirred at room temperature for 2 hours. Water (0.6 mL) was added to the reaction mixture drop-wise, followed by 2 N aqueous NaOH (0.2 mL). The reaction was stirred for another 1 hour. The solid was removed by filtration via a pack of Celite and washed with ethyl acetate. The filtrate was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 126B

tert-butyl 4-fluoro-4-((2-nitro-4-sulfamoylphenoxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 126A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 126C

tert-butyl 4-({[4-({[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]amino}sulfonyl]-2-nitrophenoxy[methyl]-4-fluoropiperidine-1-carboxylate)oxy]benzamide

The title compound was prepared by substituting EXAMPLE 126B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.36 (s, 2H), 8.02-8.06 (m, 2H), 7.49-7.53 (m, 3H), 7.40 (d, 1H), 7.35 (d, 2H), 7.04 (d, 1H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 3.83-3.85 (m, 2H), 3.09 (s, 4H),



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2.33 (s, 2H), 2.27-2.32 (m, 4H), 2.13-2.16 (m, 2H), 1.96 (s, 2H), 1.83-1.92 (m, 2H), 1.67-1.75 (m, 2H), 1.38-1.41 (m, 1H), 0.92 (s, 6H).

## Example 127

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 126C for EXAMPLE 1A in EXAMPLE 1B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.14 (d, 1H), 7.90 (d, 2H), 7.80 (dd, 1H), 7.60 (d, 1H), 7.40 (t, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 7.13 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.30 (dd, 1H), 6.26 (d, 1H), 4.28 (d, 2H), 3.10-3.13 (m, 2H), 2.91-3.00 (m, 6H), 2.73 (s, 2H), 1.96-2.02 (m, 4H), 1.77-1.89 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 128

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cyclohexyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 128A

tert-butyl 4-(tetrahydro-2H-pyran-4-yl)piperazine-1-carboxylate

The title compound was prepared by substituting tert-butyl piperazine-1-carboxylate for morpholine and dihydro-2H-pyran-4(3H)-one for tert-butyl 4-oxocyclohexylcarbamate in EXAMPLE 39A.

## Example 128B

1-(tetrahydro-2H-pyran-4-yl)piperazine dihydrochloride

To a solution of EXAMPLE 128A (3.92 g) in ether was added HCl (25 mL, 2M in ether) and the reaction mixture was stirred for 16 hours at room temperature. The solid product was filtered off, dried and used in next step without further purification.

## Example 128C

Trans-tert-butyl-4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexylcarbamate

The title compound was prepared by substituting EXAMPLE 128B for morpholine in EXAMPLE 39A.

## Example 128D

trans-4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)cyclohexanamine tris(2,2,2-trifluoroacetate)

The title compound was prepared by substituting EXAMPLE 128C for EXAMPLE 39A in EXAMPLE 39B.

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## Example 128E

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(4-tetrahydro-2H-pyran-4-yl)piperazin-1-yl]cyclohexyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 128D for EXAMPLE 100B in EXAMPLE 100C. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.28-9.32 (m, 1H), 8.44 (t, 1H), 8.34-8.39 (m, 2H), 8.10-8.14 (m, 1H), 7.66-7.69 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (t, 1H), 6.73-6.77 (m, 1H), 6.52-6.55 (m, 1H), 6.49-6.52 (m, 1H), 3.99-4.06 (m, 2H), 3.29-3.36 (m, 2H), 3.03-3.09 (m, 4H), 2.77 (s, 2H), 2.62 (s, 8H), 2.24-2.29 (m, 3H), 2.10-2.16 (m, 5H), 2.05 (s, 2H), 1.97 (s, 2H), 1.92 (s, 2H), 1.70 (d, 2H), 1.57 (td, 2H), 1.34-1.43 (m, 4H), 1.20-1.30 (m, 2H), 0.93 (s, 6H).

## Example 129

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 129A

(1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methanol

A suspension of piperidin-4-ylmethanol (0.250 g), sodium triacetoxyborohydride (0.690 g) and 1,3-difluoropropan-2-one (0.245 g) were stirred together in dichloromethane. After stirring overnight the reaction was poured into saturated aqueous NaHCO<sub>3</sub> solution (10 mL) and stirred for 15 minutes. The reaction was extracted with dichloromethane (3×25 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.75% to 3% methanol/dichloromethane gave the title compound.

## Example 129B

4-((1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

To a solution of (1-(1,3-difluoropropan-2-yl)piperidin-4-yl)methanol (0.068 g) in tetrahydrofuran (1 mL) was added sodium hydride (0.056 g) and the reaction stirred for 30 minutes at room temperature. 4-Fluoro-3-nitrobenzenesulfonamide (0.077 g) was added in one portion and stirring was continued for 1 hour. The reaction was poured into water (20 mL) and extracted with dichloromethane. The pH of the aqueous layer was adjusted to pH~8 and it was extracted with dichloromethane (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

## Example 129C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 129B for EXAMPLE 1F and EXAMPLE 3J in

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EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.47-10.98 (m, 1H), 8.33 (d, 1H), 8.03 (d, 2H), 7.50 (dd, 3H), 7.36 (t, 3H), 7.04 (d, 2H), 6.67 (d, 1H), 6.39 (dd, 1H), 6.20 (s, 1H), 4.62 (dd, 4H), 4.06 (d, 2H), 3.18-2.71 (m, 11H), 2.20 (d, 6H), 1.96 (s, 2H), 1.73 (d, 3H), 1.35 (d, 4H), 0.92 (s, 6H).

## Example 130

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 130A

(R)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 130B

(R)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

A solution of EXAMPLE 130A (550 mg) in dichloromethane (25 ml) was cooled in an ice bath under nitrogen. 2,2,2-Trifluoroacetic acid (8.333 ml) was added and the reaction was stirred for 2 hours. The product was obtained by concentration and high vacuum drying.

## Example 130C

(R)-3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 130B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 130D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 3J (90 mg), EXAMPLE 130C (64.2 mg), triethylamine (0.077 ml), N,N-dimethylpyridin-4-amine (38.5 mg) in a mixture of dichloromethane (5 ml) and N,N-dimethylformamide (0.5 ml) was added N<sup>1</sup>-((ethylimino)methylene)-N<sup>3</sup>,N<sup>3</sup>-dimethylpropane-1,3-diamine, hydrochloric acid (60.4 mg) and the mixture was stirred 18 hours. This was concentrated on high vacuum and the crude was purified by reverse phase chromatography with ammonium acetate buffer/acetonitrile. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.59 (d, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.65-7.67 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.06 (m, 1H), 3.98 (d, 2H), 3.35 (t, 2H), 3.07 (m, 4H), 2.73-2.80 (m, 4H), 2.68-2.72 (m, 1H), 2.36 (q, 1H),

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2.11-2.30 (m, 9H), 1.97 (m, 2H), 1.62-1.71 (m, 3H), 1.48-1.58 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 131

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 131A

tert-butyl(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 2,2-dimethyldihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 131B

(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 131A for EXAMPLE 130A in EXAMPLE 130B.

## Example 131C

4-((3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 131B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 131D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 131C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (d, 1H), 9.28 (m, 1H), 8.61 (m, 1H), 8.44 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.89 (m, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.07 (m, 4H), 2.71-2.82 (m, 5H), 2.37-2.44 (m, 2H), 2.19-2.29 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.32-1.49 (m, 4H), 1.28 (d, 3H), 1.20 (s, 3H), 0.94 (s, 6H).

## Example 132

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 132A

(S)-tert-butyl 1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde

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hyde and (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

**Example 132B**

(S)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 132A for EXAMPLE 130A in EXAMPLE 130B.

**Example 132C**

(S)-3-nitro-4-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 132B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 132D**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-tetrahydro-2H-pyran-4-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 132C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.04 (m, 1H), 9.27 (d, 1H), 8.58 (d, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.06 (m, 1H), 3.98 (d, 2H), 3.36 (t, 2H), 3.07 (m, 4H), 2.68-2.80 (m, 5H), 2.36 (m, 1H), 2.09-2.29 (m, 9H), 1.97 (s, 2H), 1.62-1.72 (m, 3H), 1.48-1.60 (m, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 133**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 133A**

tert-butyl(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 2,2-dimethyldihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde and (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

**Example 133B**

(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 133A for EXAMPLE 130A in EXAMPLE 130B.

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Example 133C

4-(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-ylamino)-3-nitro benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 133B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 133D**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 133C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (d, 1H), 9.28 (m, 1H), 8.61 (m, 1H), 8.43 (d, 1H), 8.38 (dd, 1H), 8.11 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.89 (m, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.49 (m, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.07 (m, 4H), 2.71-2.82 (m, 5H), 2.37-2.44 (m, 2H), 2.19-2.29 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.76 (m, 1H), 1.66 (m, 2H), 1.33-1.48 (m, 4H), 1.28 (d, 3H), 1.20 (s, 3H), 0.94 (s, 6H).

**Example 134**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-methylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 134A**

4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

A solution of EXAMPLE 113A (0.8 g) in dichloromethane (10 mL) and trifluoroacetic acid (10 mL) was stirred at room temperature for 2 hours. The solvents were evaporated and the residue triturated with diethyl ether. The resulting solid was dissolved in 5% aqueous sodium carbonate solution (20 mL). The solution was concentrated to dryness and the resulting solid was triturated with a solution of 10% methanol in dichloromethane several times. Evaporation of the organic solvents gave the title compound.

**Example 134B**

4-((4-methylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 134A (158 mg) in anhydrous N,N-dimethylformamide (4 mL) was added sodium carbonate (64 mg) and methyl iodide (78 mg). After stirring overnight at room temperature, the mixture was evaporated to dryness. The crude product was then absorbed on silica gel (6 g) and purified on a silica gel column eluting with 10% methanol in dichloromethane to give the title compound.

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## Example 134C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 134B for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.92 (m, 1H), 3.86 (d, 1H), 3.67 (dt, 1H), 3.49-3.39 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 3.71 (m, 1H), 2.49 (d, 1H), 2.26 (m, 2H), 2.16 (s, 3H), 2.14 (m, 4H), 2.03 (dt, 1H), 1.97 (s, 2H), 1.90 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 135

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 135A

4-((4-(2-methoxyethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-methoxyethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 135B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(2-methoxyethyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 135A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.98 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.93 (m, 1H), 3.87 (d, 1H), 3.70 (dt, 1H), 3.51 (t, 2H), 3.48-3.38 (m, 2H), 3.27 (s, 3H), 3.07 (m, 4H), 2.95 (d, 1H), 2.77 (s, 2H), 2.70 (m, 1H), 2.57 (t, 2H), 2.27-2.07 (m, 8H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 136

N-[(4-{[4-(acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 136A

4-((4-(acetylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting acetic anhydride for methyl iodide in EXAMPLE 134B.

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## Example 136B

N-[(4-{[4-(acetylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 136A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (s, 1H), 8.85 (s, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.10 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (dd, 1H), 6.75 (dd, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.73 (dd, 1H), 3.93-3.65 (m, 2H), 3.60-3.40 (m, 4H), 3.12 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.57 (t, 2H), 2.14 (s, 3H), 2.27-2.07 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 137

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 137A

ethyl 4-fluorobut-2-enoate

Ethyl 2-fluoroacetate (21.0 g) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at -78° C. was treated dropwise over 45 min with a 1.0 M solution of diisobutylaluminum hydride in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) maintaining the internal temperature below -70° C. Stirring was continued at -78° C. for 30 minutes and then (carbethoxymethylene)triphenylphosphorane (70.0 g) was added in one portion. The reaction mixture was allowed to slowly reach room temperature while stirring overnight. It was then quenched with methanol, filtered and concentrated to give the product as a mixture of isomers (E/Z=3:1).

## Example 137B

Trans-ethyl

1-benzyl-4-(fluoromethyl)pyrrolidine-3-carboxylate

A mixture of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (4.5 g) and EXAMPLE 137A (2.5 g) in dichloromethane (50 mL) was cooled to 0° C., treated dropwise with trifluoroacetic acid (0.15 mL), stirred for 4 hours at 0° C. and neutralized with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution. The mixture was poured into a separatory funnel and the layers separated. The organic layer was washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 0-20% ethyl acetate in hexanes as eluent to give both the cis and trans isomers of the product. Only the trans diastereomers were carried on in the following steps.

## Example 137C

Trans-ethyl

4-(fluoromethyl)pyrrolidine-3-carboxylate

EXAMPLE 137B (0.83 g) in ethanol (9 mL) was treated with 10% Pd/C (0.208 g) and ammonium formate (1.97 g), refluxed for 1.5 hours, concentrated, dissolved in dichlo-



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romethane, filtered through a pad of celite rinsing with dichloromethane, and concentrated to give the product.

## Example 137D

Trans-1-benzyl 3-ethyl  
4-(fluoromethyl)pyrrolidine-1,3-dicarboxylate

EXAMPLE 137C (0.44 g) in dioxane (4 mL) and water (4 mL) at 0° C. was treated sequentially with Na<sub>2</sub>CO<sub>3</sub> (0.89 g) and benzyl chloroformate (0.48 mL). The reaction mixture was stirred at 0° C. for 3 hours and was then allowed to slowly warm to room temperature over 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 10-25% ethyl acetate in hexanes as eluent to give the product.

## Example 137E

Trans-1-(benzyloxycarbonyl)-4-(fluoromethyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by substituting EXAMPLE 137D for EXAMPLE 15G in EXAMPLE 15H.

## Example 137F

Trans-benzyl 3-(fluoromethyl)-4-(hydroxymethyl)  
pyrrolidine-1-carboxylate

EXAMPLE 137E (0.563 g) in tetrahydrofuran (10 mL) at 0° C. was treated dropwise with a 1 M solution of borane in tetrahydrofuran (4 mL), stirred for 3 hours and then slowly quenched with saturated aqueous NH<sub>4</sub>Cl solution. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated to give the product.

## Example 137G

Trans-benzyl 3-(fluoromethyl)-4-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 137F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 137H

Trans-4-((4-(fluoromethyl)pyrrolidin-3-yl)methoxy)-  
3-nitrobenzenesulfonamide

EXAMPLE 137G (0.232 g) in acetic acid (2.5 mL) was treated with hydrobromic acid (33 wt % in acetic acid) (0.875 mL) at ambient temperature, stirred for 1 hour and concentrated. The product was free-based using a MEGA BE-SCX column with 1:1 CH<sub>2</sub>Cl<sub>2</sub>/methanol as eluent for the hydrobromic acid and acetic acid. The product was released from the column with 10% (7 M ammonia in methanol) in CH<sub>2</sub>Cl<sub>2</sub> as eluent.

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## Example 137I

Trans-4-((4-(fluoromethyl)-1-(oxetan-3-yl)pyrrolidin-3-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 137H for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 137J

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([trans-4-(fluoromethyl)-1-oxetan-3-ylpyrrolidin-3-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 137I for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.35 (d, 1H), 8.03 (m, 2H), 7.51 (m, 3H), 7.37 (m, 3H), 7.04 (m, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.45 (m, 6H), 4.21 (d, 2H), 3.62 (m, 1H), 3.08 (m, 4H), 2.72 (m, 5H), 2.31 (m, 9H), 1.96 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 138

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 138A

(4-fluorotetrahydro-2H-pyran-4-yl)methyl  
methanesulfonate

A mixture of EXAMPLE 37C (1.4 g), methanesulfonyl chloride (1.054 mL), triethylamine (2.99 mL), and 4-dimethylaminopyridine (0.051 g) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was stirred at 0° C. for 2 hours, concentrated and chromatographed on silica gel eluting with 30% ethyl acetate in hexanes to give the product.

## Example 138B

2-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)isoindoline-1,3-dione

A mixture of EXAMPLE 138A (1.8 g) and potassium phthalimide (2.356 g) in N,N-dimethylformamide (30 mL) was heated at 150° C. overnight, diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel eluting with 30% ethyl acetate in hexanes to give the product.

## Example 138C

(4-fluorotetrahydro-2H-pyran-4-yl)methanamine

A mixture of EXAMPLE 138B (1.4 g) and hydrazine (1.548 mL) in ethanol (40 mL) was heated at 70° C. overnight, cooled to room temperature, slurried with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and the solid removed by filtration. The filtrate was concen-

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trated and chromatographed on silica gel eluting with 100:5:1 ethyl acetate/methanol/ $\text{NH}_4\text{OH}$  to give the product.

## Example 138D

4-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (0.44 g), EXAMPLE 138C (0.266 g), and triethylamine (1.11 mL) in tetrahydrofuran (10 mL) was heated at 70° C. overnight, diluted with ethyl acetate, washed with water and brine, dried ( $\text{MgSO}_4$ ), filtered, concentrated and chromatographed on silica gel eluting with 50% ethyl acetate in hexanes to give the product.

## Example 138E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 138D for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.68 (s, 1H), 8.62 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.82 (dd, 1H), 7.48-7.54 (m, 3H), 7.34 (d, 2H), 7.24 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.70-3.77 (m, 4H), 3.50-3.55 (m, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.14-2.20 (m, 6H), 1.76-1.84 (m, 4H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 139

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 139A

tert-butyl 4-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfonyl)-2-nitrophenylamino)piperidine-1-carboxylate

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetyl piperidin-4-amine with 4-amino-piperidine-1-carboxylic acid tert-butyl ester.

## Example 139B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylamino)phenylsulfonyl)benzamide

To a cooled (0° C.) solution of EXAMPLE 139A (960 mg) in dichloromethane (10 mL) was added dropwise trifluoroacetic acid (5 mL). The mixture was stirred at the temperature for 3 hours. Then, the mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (200 mL) and washed with aqueous  $\text{NaHCO}_3$  and brine. After drying over  $\text{Na}_2\text{SO}_4$ , the mixture was filtered, and evaporation of the solvent from the filtrate gave the title compound.

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## Example 139C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 139B (120 mg) in tetrahydrofuran (3 mL) and acetic acid (1 mL) was added oxetan-3-one (50.8 mg) and MP-cyanoborohydride (2.15 mmol/g, 150 mg). The mixture was stirred at room temperature overnight. The mixture was filtered. The filtrate was concentrated and the residue was loaded on a silica gel cartridge and eluted with 5-10% 7N  $\text{NH}_3$  in methanol in dichloromethane to give the title compound.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.62 (s, 1H), 8.51 (d, 1H), 8.20 (d, 1H), 7.99 (d, 1H), 7.74 (m, 1H), 7.48 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.36 (dd, 1H), 6.20 (d, 1H), 4.54 (t, 2H), 4.43 (t, 2H), 3.66 (m, 1H), 3.44 (m, 3H), 3.04 (m, 5H), 2.73 (s, 2H), 2.61 (m, 2H), 2.12 (m, 11H), 1.61 (m, 2H), 1.38 (t, 2H), 0.93 (m, 6H).

## Example 140

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclobutyl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with cyclobutanone.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.58 (s, 1H), 8.47 (d, 1H), 8.12 (d, 1H), 7.97 (d, 1H), 7.74 (d, 1H), 7.53 (d, 1H), 7.45 (m, 1H), 7.36 (m, 3H), 7.02 (m, 3H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.22 (d, 1H), 3.74 (m, 1H), 2.97 (m, 6H), 2.73 (s, 3H), 2.15 (m, 15H), 1.67 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

## Example 141

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)piperidin-4-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with 2,2-dimethyltetrahydropyran-4-one.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.60 (s, 1H), 8.50 (d, 1H), 8.15 (m, 1H), 7.99 (d, 1H), 7.78 (m, 1H), 7.62 (m, 1H), 7.47 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.65 (m, 2H), 6.35 (dd, 1H), 6.21 (d, 1H), 4.56 (d, 3H), 3.89 (m, 3H), 3.67 (m, 6H), 3.45 (m, 2H), 3.04 (m, 3H), 2.75 (m, 3H), 2.14 (m, 3H), 1.71 (m, 5H), 1.16 (s, 9H).

## Example 142

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 142A

(S)-tert-butyl 1-cyclopropylpyrrolidin-3-ylcarbamate

(S)-tert-butyl pyrrolidin-3-ylcarbamate (415 mg), (1-ethoxycyclopropoxy)trimethylsilane (1.8 mL) and

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molecular sieves (500 mg) were combined in methanol (4.5 mL). Acetic acid (1.3 mL) was added, followed by sodium cyanoborohydride (420 mg). The resulting mixture was heated to reflux for 4 hours. Insoluble material was filtered off and reaction was made basic to pH 14 with addition of 6M aqueous NaOH solution. The solution was extracted three times with diethyl ether, and the combined extracts were dried over MgSO<sub>4</sub>, filtered and concentrated to obtain an oil, which was purified by flash chromatography, eluting first with 100% dichloromethane, followed by 5% methanol/dichloromethane and 10% methanol/dichloromethane.

## Example 142B

## (S)-1-cyclopropylpyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 142A for EXAMPLE 1A in EXAMPLE 1B.

## Example 142C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 142B for 1-acetylpyrrolidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.51 (m, 2H), 8.30 (m, 1H), 8.00 (br s, 1H), 7.77 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.97 (br s, 1H), 6.67 (dd, 1H), 6.36 (m, 1H), 6.21 (m, 1H), 4.19 (m, 1H), 3.00 (m, 5H), 2.74 (m, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.15 (m, 6H), 1.95 (s, 2H), 1.78 (br s, 1H), 1.68 (m, 1H), 1.38 (t, 2H), 1.23 (m, 1H), 0.92 (s, 6H), 0.39 (m, 4H).

## Example 143

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-tetrahydro furan-3-yl)piperidin-4-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing oxetan-3-one with 3-oxotetrahydrofuran. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.53 (d, 1H), 8.21 (m, 1H), 8.02 (m, 1H), 7.80 (dd, 1H), 7.49 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.67 (dd, 1H), 6.37 (m, 1H), 6.19 (d, 1H), 4.29 (m, 3H), 3.73 (m, 6H), 3.09 (m, 4H), 2.76 (m, 2H), 2.05 (m, 8H), 1.68 (m, 2H), 1.37 (m, 2H), 0.94 (s, 6H).

## Example 144

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 144A

## (R)-tert-butyl 1-cyclopropylpyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for (S)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 142A.

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## Example 144B

## (R)-1-cyclopropylpyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 144A for EXAMPLE 1A in EXAMPLE 1B.

## Example 144C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-cyclopropylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 144B for 1-acetylpyrrolidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.53 (d, 2H), 8.32 (d, 1H), 8.02 (d, 1H), 7.81 (m, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.37 (m, 1H), 6.20 (d, 1H), 4.21 (m, 1H), 3.00 (m, 5H), 2.74 (m, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.15 (m, 6H), 1.95 (s, 2H), 1.74 (br s, 1H), 1.66 (m, 1H), 1.38 (t, 2H), 1.23 (m, 1H), 0.92 (s, 6H), 0.39 (m, 4H).

## Example 145

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-nitro-4-[(3S)-1-tetrahydro-2H-pyran-4-yl]pyrrolidin-3-yl]methyl}amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 145A

(S)-tert-butyl(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 145B

(S)-(1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 145A for EXAMPLE 1A in EXAMPLE 1B.

## Example 145C

(S)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-((1-(tetrahydro-2H-pyran-4-yl)pyrrolidin-3-yl)methylamino)phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 145B for 1-acetylpyrrolidin-4-amine in

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EXAMPLE 53B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.61 (br s, 1H), 8.46 (s, 1H), 7.96 (d, 1H), 7.72 (m, 1H), 7.54 (d, 1H), 7.45 (t, 1H), 7.37 (br s, 2H), 7.34 (d, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.22 (d, 1H), 3.89 (m, 2H), 3.38 (m, 4H), 3.27 (m, 4H), 3.02 (m, 5H), 2.73 (s, 2H), 2.61 (m, 1H), 2.18 (m, 6H), 2.05 (m, 1H), 1.95 (m, 2H), 1.85 (m, 2H), 1.64 (m, 1H), 1.50 (m, 2H), 1.38 (m, 2H), 0.94 (s, 6H).

## Example 146

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxy-2,2-dimethylpropyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using 3-amino-2,2-dimethylpropan-1-ol in place of EXAMPLE 120A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.35 (s, 1H), 8.96 (t, 1H), 8.56 (d, 1H), 8.05 (d, 1H), 7.79 (dd, 1H), 7.46-7.56 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 5.10 (t, 1H), 3.29 (d, 1H), 3.24 (d, 1H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.93 (d, 12H).

## Example 147

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-(methylsulfonyl)piperidin-3-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 147A

tert-butyl(1-(methylsulfonyl)piperidin-3-yl)methylcarbamate

tert-Butyl piperidin-3-ylmethylcarbamate (500 mg) was dissolved in anhydrous dichloromethane (10 mL), and methanesulfonyl chloride (0.181 mL) was added followed by the addition of triethylamine (1.3 mL). The reaction mixture was stirred at room temperature overnight. The organic solvent was removed under vacuum. The residue was purified with flash column chromatography on silica gel eluting with 0-70% ethyl acetate in hexane to give the title compound.

## Example 147B

(1-(methylsulfonyl)piperidin-3-yl)methanamine

EXAMPLE 147A (400 mg) was suspended in 4N HCl in dioxane (10 mL) followed by the addition of anhydrous methanol (1 mL). The clear solution was stirred at room temperature for 2 hours. The organic solvent was removed under vacuum. The solid residue was used in the next step without further purification.

## Example 147C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-(methylsulfonyl)piperidin-3-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 53A (50 mg), EXAMPLE 147B (26 mg) and triethylamine (0.088 mL) were dissolved in anhydrous diox-

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ane (1 mL) and N,N-dimethylformamide (0.2 mL). The reaction vial was heated in a Biotage Initiator microwave reactor at 130° C. for 25 minutes. The solvent was removed under vacuum. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 20-80% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound as the trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.52 (m, 1H), 3.40 (m, 2H), 3.06 (m, 4H), 2.84 (s, 3H), 2.75 (m, 2H), 2.75 (m, 4H), 2.58 (m, 1H), 2.16 (m, 6H), 1.95 (s, 3H), 1.76 (m, 2H), 1.52 (m, 1H), 1.37 (m, 2H), 0.92 (s, 6H).

## Example 148

N-([4-([1-(acetyl)piperidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 148A

tert-butyl(1-(acetyl)piperidin-3-yl)methylcarbamate

The title compound was prepared by substituting acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

## Example 148B

1-(3-(aminomethyl)piperidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 148A for EXAMPLE 147A in EXAMPLE 147B.

## Example 148C

N-([4-([1-(acetyl)piperidin-3-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 148B for EXAMPLE 147B in EXAMPLE 147C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.56 (m, 2H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.12 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 3.07 (m, 4H), 2.89 (m, 1H), 2.71 (m, 2H), 2.16 (m, 6H), 1.96 (s, 3H), 1.80 (m, 4H), 1.38 (t, 2H), 1.27 (m, 2H), 0.92 (s, 6H).



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## Example 149

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 149A

(R)-tert-butyl  
1-(methylsulfonyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate in EXAMPLE 147A.

## Example 149B

(R)-1-(methylsulfonyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 149A for EXAMPLE 147A in EXAMPLE 147B.

## Example 149C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 149B for EXAMPLE 147B in EXAMPLE 147C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 8.02 (d, 1H), 7.86 (dd, 1H), 7.49 (m, 3H), 7.33 (d, 2H), 7.17 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.41 (m, 1H), 3.69 (m, 1H), 3.39 (m, 3H), 3.06 (m, 4H), 2.97 (s, 3H), 2.76 (m, 2H), 2.27 (m, 8H), 1.93 (m, 2H), 1.54 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 150

4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 150A

Ethyl  
2-hydroxy-3,3-dimethylcyclohex-1-enecarboxylate

Into a 500 mL round-bottomed flask was added diisopropylamine (3.5 mL) in ether (200 mL). After cooling to -30° C., butyllithium (16 mL) (1.6M in hexane) was added slowly. After stirring 30 minutes, the temperature was cooled to -5° C. 2,2-Dimethylcyclohexanone (3 g) was added slowly. The mixture was warmed up to 0° C. and stirred for 1 hour. After cooling to -5° C., hexamethylphosphoramide (8 mL) and ethyl carbonocyanide (2.5 mL) were added. After stirring at -5° C. for 20 minutes, and warming to room temperature, the reaction was stirred for 1 hour. The mixture was poured into cold water, and the layers were separated. The aqueous layer was extracted with ether (3×20 mL). The combined the

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organic layers were washed with saturated aqueous NH<sub>4</sub>Cl (3×20 mL). After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography on silica with 0-10% ethyl acetate in hexanes to provide the title compound.

## Example 150B

Ethyl 3,3-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 150A for EXAMPLE 101A in EXAMPLE 101B.

## Example 150C

Ethyl 2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enecarboxylate

The title compound was prepared by substituting EXAMPLE 150B for EXAMPLE 101B in EXAMPLE 101C.

## Example 150D

(2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methanol

In a 200 mL round-bottomed flask was added EXAMPLE 150C (0.97 g) and lithium borohydride (0.47 g) in ether (20 mL) to give a suspension. Methanol (2.2 mL) was added slowly. The mixture was refluxed overnight. The reaction was then cooled, and methanol was added to quench the reaction. 1N aqueous HCl was then added until the pH<7, and ether (3×30 mL) was used to extract the product. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was purified by flash chromatography on silica with 0-25% ethyl acetate in hexanes to provide the title compound.

## Example 150E

2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enecarbaldehyde

Into a 100 mL round-bottomed flask was added EXAMPLE 150D (0.3 g) and Dess-Martin Periodinane (0.6 g) in dichloromethane (10 mL) to give a suspension. The mixture was stirred at room temperature overnight. After filtration, the mixture was washed with saturated aqueous NaHCO<sub>3</sub> (2×20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by flash chromatography on silica with 0-25% ethyl acetate in hexanes to provide the title compound.

## Example 150F

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-enyl)methylpiperazin-1-ylbenzoate

The title compound was prepared by substituting EXAMPLE 150E for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

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## Example 150G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 150F for EXAMPLE 101E in EXAMPLE 101F.

## Example 150H

4-(4-{[2-(4-chlorophenyl)-3,3-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 150G for EXAMPLE 3J and EXAMPLE 1F for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethyl sulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.36 (m, 1H), 8.32 (m, 1H), 7.91 (d, 1H), 7.59 (m, 2H), 7.40 (t, 1H), 7.35 (d, 2H), 7.25 (m, 1H), 6.94 (d, 2H), 6.79 (d, 1H), 6.60 (m, 1H), 6.29 (m, 1H), 6.24 (d, 1H), 3.83 (m, 2H), 3.25 (m, 4H), 2.98 (m, 4H), 2.42 (s, 2H), 2.14 (m, 6H), 1.60 (m, 6H), 1.25 (m, 3H), 0.86 (s, 6H)

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4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 151A

1-(1,3-difluoropropan-2-yl)azetidin-3-amine

To a solution of tert-butyl azetidin-3-ylcarbamate (0.256 g) and 1,3-difluoropropan-2-one (0.154 g) in dichloromethane (2 mL) was added sodium triacetoxyborohydride (0.473 g) and the reaction was allowed to stirred at room temperature. After 16 hours, the reaction was quenched with saturated NaHCO<sub>3</sub> solution (10 mL) and extracted into dichloromethane (25 mL). The organic layer was dried and concentrated. Silica gel chromatography (GraceResolv 12 g) eluting with a gradient of 0.5% to 3.5% methanol/dichloromethane followed by treatment with HCl (4.0M in dioxane, 3 mL) and methanol (0.5 mL) for 2 hours gave the title compound after concentration.

## Example 151B

4-(1-(1,3-difluoropropan-2-yl)azetidin-3-ylamino)-3-nitrobenzenesulfonamide

To a suspension of 4-chloro-3-nitrobenzenesulfonamide (0.225 g) and 1-(1,3-difluoropropan-2-yl)azetidin-3-amine (0.193 g) in dioxane (5 mL) was added diisopropylamine (0.832 mL). The reaction was sonicated and then heated to 100° C. After stirring overnight, the reaction was concentrated and loaded onto silica gel (GraceResolv 12 g) and eluted with a gradient of 0.5% to 3.5% methanol/dichloromethane to give the title compound.

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## Example 151C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 151B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.54-11.28 (m, 1H), 8.54 (d, 1H), 8.45 (s, 1H), 8.01 (d, 1H), 7.82 (d, 1H), 7.48 (d, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.90 (d, 1H), 6.67 (d, 1H), 6.37 (s, 1H), 6.20 (s, 1H), 4.64-4.23 (m, 6H), 3.81 (s, 2H), 3.08 (s, 4H), 2.75 (s, 3H), 2.15 (s, 7H), 1.95 (s, 2H), 1.38 (s, 2H), 0.92 (s, 6H).

## Example 152

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-(methylsulfonyl)pyrrolidin-3-yl}methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 152A

tert-butyl(1-(methylsulfonyl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate in EXAMPLE 147A.

## Example 152B

(1-(methylsulfonyl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 152A for EXAMPLE 147A in EXAMPLE 147B.

## Example 152C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({1-(methylsulfonyl)pyrrolidin-3-yl}methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 152B for EXAMPLE 147B in EXAMPLE 147C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.49 (m, 2H), 7.99 (s, 1H), 7.73 (m, 1H), 7.53 (d, 1H), 7.47 (s, 1H), 7.42 (m, 1H), 7.34 (d, 2H), 7.04 (m, 3H), 6.65 (m, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 3.41 (m, 4H), 3.22 (m, 2H), 3.03 (m, 4H), 2.89 (s, 3H), 2.73 (m, 2H), 2.59 (m, 1H), 2.17 (m, 6H), 2.00 (m, 4H), 1.68 (m, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

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## Example 153

N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 153A

tert-butyl(1-acetylpyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate and acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

## Example 153B

1-(3-(aminomethyl)pyrrolidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 153A for EXAMPLE 147A in EXAMPLE 147B.

## Example 153C

N-[(4-{[(1-acetylpyrrolidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 153B for EXAMPLE 147B in EXAMPLE 147C. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.62 (m, 1H), 8.54 (s, 1H), 8.03 (m, 1H), 7.78 (d, 1H), 7.50 (m, 3H), 7.35 (t, 2H), 7.09 (s, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.20 (s, 1H), 3.56 (m, 1H), 3.42 (m, 4H), 3.43 (m, 4H), 3.23 (m, 1H), 3.07 (m, 4H), 2.74 (m, 2H), 2.16 (m, 6H), 1.93 (m, 5H), 1.38 (t, 2H), 0.93 (s, 6H).

## Example 154

N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 154A

(R)-tert-butyl 1-acetylpyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperidin-3-ylmethylcarbamate and acetyl chloride for methanesulfonyl chloride in EXAMPLE 147A.

## Example 154B

(R)-1-(3-aminopyrrolidin-1-yl)ethanone

The title compound was prepared by substituting EXAMPLE 154A for EXAMPLE 147A in EXAMPLE 147B.

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## Example 154C

N-[(4-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 154B for EXAMPLE 147B in EXAMPLE 147. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (s, 1H), 8.50 (s, 1H), 8.17 (d, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.10 (m, 1H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 4.34 (m, 1H), 3.81 (m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 3.05 (m, 4H), 2.74 (s, 2H), 2.19 (m, 9H), 1.96 (m, 5H), 1.38 (t, 2H), 0.94 (s, 6H).

## Example 155

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{4-{[3-methoxy-2,2-dimethylpropyl]amino}-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using 3-methoxy-2,2-dimethylpropan-1-amine in place of EXAMPLE 120A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.32 (s, 1H), 8.92 (t, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.46-7.55 (m, 3H), 7.34 (d, 2H), 7.08 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.36-6.42 (m, 1H), 6.19 (d, 1H), 3.25-3.30 (m, 5H), 3.19 (s, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.96 (s, 6H), 0.92 (s, 6H).

## Example 156

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{4-{[(1R,3R)-3-hydroxycyclopentyl]methyl}amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 156A

4-(((1R,3R)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1R,3R)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 156B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{4-{[(1R,3R)-3-hydroxycyclopentyl]methyl}amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 156A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.29 (s, 1H), 8.62 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.85 (d, 1H), 6.74 (dd, 1H), 6.54 (s, 1H), 6.49 (m, 1H), 4.60 (m, 1H), 3.19 (dd, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (t, 2H),

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2.20-2.07 (m, 6H), 2.00 (m, 1H), 1.97 (s, 2H), 1.90 (m, 1H),  
1.56 (m, 1H), 1.39 (t, 2H), 1.34 (m, 1H), 0.93 (s, 6H).

## Example 157

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 157A

4-(((1S,3S)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1S,3S)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 157B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 157A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.29 (s, 1H), 8.60 (t, 1H), 8.44 (d, 1H), 8.32 (dd, 1H), 8.14 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.55 (s, 1H), 6.49 (m, 1H), 4.60 (m, 1H), 3.19 (dd, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.70 (m, 1H), 2.26 (t, 2H), 2.20-2.07 (m, 6H), 2.00 (m, 1H), 1.97 (s, 2H), 1.90 (m, 1H), 1.56 (m, 1H), 1.39 (t, 2H), 1.34 (m, 1H), 0.93 (s, 6H).

## Example 158

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 158A

4-(((1S,3R)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1S,3R)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 158B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1S,3R)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 158A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.94 (s, 1H), 9.25 (d, 1H), 8.59 (t, 1H), 8.48 (d, 1H), 8.27 (m, 2H), 7.66 (m, 2H),

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7.45 (d, 2H), 7.08 (d, 2H), 6.77 (dd, 1H), 6.72 (d, 1H), 6.60 (d, 1H), 6.47 (m, 1H), 4.53 (m, 1H), 3.30 (m, 2H), 3.06 (m, 4H), 2.78 (s, 2H), 2.27 (m, 3H), 2.19-2.10 (m, 5H), 1.98 (m, 3H), 1.85-1.66 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 159

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 159A

4-(((1R,3S)-3-hydroxycyclopentyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (1R,3S)-3-hydroxycyclopentyl)methylamine for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 159B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(1R,3S)-3-hydroxycyclopentyl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 159A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (s, 1H), 9.28 (d, 1H), 8.59 (t, 1H), 8.44 (d, 1H), 8.29 (d, 1H), 8.13 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.08 (d, 2H), 6.82 (dd, 1H), 6.74 (d, 1H), 6.55 (d, 1H), 6.48 (m, 1H), 4.53 (m, 1H), 3.34 (m, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.27 (m, 3H), 2.19-2.10 (m, 5H), 1.97 (m, 3H), 1.85-1.66 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 160

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-2-oxopiperidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (S)-3-aminopiperidin-2-one for 1-acetyl piperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (br s, 1H), 8.88 (d, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.95 (br s, 1H), 7.83 (dd, 1H), 7.55-7.46 (m, 3H), 7.35 (d, 2H), 7.16 (d, 1H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.21 (d, 1H), 4.41 (m, 1H), 3.22 (m, 2H), 3.09 (br s, 4H), 2.78 (br s, 2H), 2.35-2.09 (m, 8H), 1.96 (br s, 2H), 1.86 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).



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## Example 161

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 161A

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfonyl)-2-nitrophenylamino)methyl)azetidine-1-carboxylate

EXAMPLE 82 (305 mg), tert-butyl 3-(aminomethyl)azetidine-1-carboxylate (86 mg) and diisopropyl amine (0.202 mL) in dioxane (3 mL) were heated to 110° C. After stirring overnight, the reaction was concentrated. Silica gel chromatography (Reveleris, 12 g) eluting with a gradient of 0.5% to 3% methanol/dichloromethane (Flow=36 ml/minute) gave the title compound.

## Example 161B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(azetidin-3-ylmethylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

To a solution of EXAMPLE 161A (0.257 g) in dichloromethane (5 mL) was added trifluoroacetic acid (0.211 mL). After 30 minutes an additional 0.2 mL of trifluoroacetic acid was added. After 3 hours, the reaction was concentrated to give the title compound.

## Example 161C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]azetidin-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A solution of EXAMPLE 161B (0.118 g), sodium triacetoxyborohydride (0.035 g) and 1,3-difluoropropan-2-one (0.012 g) were stirred together in dichloromethane (1 mL) overnight. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> solution (10 mL) and extracted into dichloromethane (30 mL). The organic layer was dried and concentrated. Silica gel chromatography (Reveleris 12 g) eluting with a gradient of 0.5% to 3.5% methanol/dichloromethane over 30 minutes (Flow=36 ml/min) gave the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.47-11.21 (m, 1H), 8.85 (s, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.80 (dd, 1H), 7.54-7.45 (m, 3H), 7.33 (s, 2H), 7.04 (d, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.43 (dt, 4H), 3.56 (t, 2H), 3.46 (s, 2H), 3.12 (m, 6H), 2.74 (m, 3H), 2.17 (m, 7H), 1.95 (s, 2H), 1.39 (d, 2H), 0.92 (s, 6H).

## Example 162

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-oxetan-3-ylazetidin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 161C. <sup>1</sup>H

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NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.51-11.03 (m, 1H), 8.81 (s, 1H), 8.54 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.50 (dd, 3H), 7.34 (d, 2H), 7.04 (d, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.57 (s, 2H), 4.43-4.35 (m, 2H), 3.82 (s, 1H), 3.59 (t, 2H), 3.44 (t, 2H), 3.20 (s, 2H), 3.06 (s, 4H), 2.73 (s, 3H), 2.18 (s, 6H), 1.95 (s, 2H), 1.39 (d, 2H), 0.92 (s, 6H).

## Example 163

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 163A

tert-butyl 4-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfonyl)-2-nitrophenylamino)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 4-(aminomethyl)piperidine-1-carboxylate for 1-acetylpiperidin-4-amine in EXAMPLE 53B.

## Example 163B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylmethylamino)phenyl)sulfonylbenzamide

The title compound was prepared by substituting EXAMPLE 163A for EXAMPLE 1A in EXAMPLE 1B.

## Example 163C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-[(1-oxetan-3-ylpiperidin-4-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 163B for EXAMPLE 161B and oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 161C. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.60 (t, 1H), 8.54 (d, 1H), 8.03 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.09 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.55 (t, 2H), 4.46 (t, 2H), 3.52 (br s, 1H), 3.28 (m, 2H), 3.17 (d, 1H), 3.06 (m, 4H), 2.82 (m, 2H), 2.74 (m, 2H), 2.17 (m, 6H), 1.95 (m, 3H), 1.72 (m, 3H), 1.38 (t, 2H), 1.28 (m, 2H), 0.92 (s, 6H).

## Example 164

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-[(1-cyclopropylpiperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 163B for (S)-tert-butyl pyrrolidin-3-ylcarbamate

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in EXAMPLE 142A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.96 (br s, 1H), 11.62 (br s, 1H), 8.50 (m, 2H), 7.98 (d, 1H), 7.72 (m, 1H), 7.52 (d, 1H), 7.45 (m, 2H), 7.34 (d, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.22 (d, 1H), 3.28 (m, 3H), 3.04 (m, 5H), 2.72 (s, 2H), 2.64 (m, 1H), 2.64 (m, 1H), 2.36 (m, 1H), 2.16 (m, 7H), 1.95 (s, 2H), 1.68 (m, 3H), 1.38 (t, 2H), 1.18 (m, 3H), 0.94 (s, 6H), 0.35 (m, 3H).

## Example 165

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-(2-fluoroethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 165A

4-((4-(2-fluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-fluoroethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 165B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-(2-fluoroethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 165A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 3.93 (m, 1H), 4.63, 4.51 (dt, 2H), 3.95-3.85 (m, 2H), 3.68 (dt, 1H), 3.43-3.37 (m, 2H), 3.07 (m, 4H), 2.92 (d, 1H), 2.77 (s, 2H), 2.65 (m, 2H), 2.59 (m, 1H), 2.26 (m, 2H), 2.17-2.08 (m, 5H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 166

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-(2,2-difluoroethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 166A

4-((4-(2,2-difluoroethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2,2-difluoroethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 166B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-(2,2-difluoroethyl)morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 166A for EXAMPLE 130C in EXAMPLE

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130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.93 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 6.31, 6.20, 6.09 (tt, 1H), 3.90 (m, 1H), 3.85 (d, 1H), 3.67 (dt, 1H), 3.49-3.30 (m, 2H), 3.07 (m, 4H), 2.84 (d, 1H), 2.82-2.75 (m, 4H), 2.69 (d, 1H), 2.33 (dt, 1H), 2.27-2.20 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 167

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-(4-fluoro-1-oxetan-3-yl)piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 167A

4-((4-(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 173A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 167B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-(4-fluoro-1-oxetan-3-yl)piperidin-4-yl)methoxy]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 167A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.39 (s, 1H), 8.09 (d, 1H), 8.04 (d, 1H), 7.52 (m, 4H), 7.35 (d, 2H), 7.05 (m, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (s, 1H), 4.57 (t, 2H), 4.48 (m, 2H), 4.38 (d, 2H), 4.02 (m, 1H), 3.63 (m, 2H), 3.08 (m, 4H), 2.74 (m, 4H), 2.17 (m, 6H), 1.88 (m, 6H), 1.40 (t, 2H), 0.93 (s, 6H).

## Example 168

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-4,4-difluoro-1-oxetan-3-yl]pyrrolidin-2-yl}methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 168A

(S)-methyl 4,4-difluoropyrrolidine-2-carboxylate

(S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate (0.472 g) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was treated with trifluoroacetic acid (1.4 mL), stirred at ambient temperature for 4 hours, and concentrated. The product was free-based using a MEGA BE-SCX column with 1:1 CH<sub>2</sub>Cl<sub>2</sub>/methanol

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as eluent for the trifluoroacetic acid. The product was released from the column with 5% (7 M ammonia in methanol) in CH<sub>2</sub>Cl<sub>2</sub> as eluent.

## Example 168B

(S)-methyl 4,4-difluoro-1-(oxetan-3-yl)pyrrolidine-2-carboxylate

The title compound was prepared by substituting EXAMPLE 168A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 168C

(S)-(4,4-difluoro-1-(oxetan-3-yl)pyrrolidin-2-yl) methanol

Example 168B (0.180 g) in tetrahydrofuran (3 mL) was treated sequentially with a solution of calcium chloride (0.245 g) in ethanol (3 mL) and NaBH<sub>4</sub> (0.167 g) and then stirred at ambient temperature for 7 hours. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl solution and extracted with ethyl acetate. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 50% ethyl acetate in hexanes as eluent to give the product.

## Example 168D

(S)-4-((4,4-difluoro-1-(oxetan-3-yl)pyrrolidin-2-yl) methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 168C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 168E

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-((2S)-4,4-difluoro-1-oxetan-3-ylpyrrolidin-2-yl)methoxy)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 168D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.38 (s, 1H), 8.06 (m, 2H), 7.49 (m, 4H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.21 (s, 1H), 4.54 (m, 3H), 4.43 (t, 1H), 4.23 (m, 1H), 4.12 (m, 2H), 3.44 (m, 2H), 3.12 (m, 7H), 2.58 (m, 1H), 2.29 (m, 7H), 1.97 (s, 2H), 1.40 (t, 2H), 0.93 (s, 6H).

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## Example 169

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-((4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methyl)amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 169A

tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared as described in EXAMPLE 53B by replacing 1-acetylpiperidin-4-amine with tert-butyl 3-(aminomethyl)morpholine-4-carboxylate.

## Example 169B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-(morpholin-3-ylmethylamino)-3-nitrophenyl)sulfonylbenzamide

The title compound was prepared as described in EXAMPLE 139B by replacing EXAMPLE 139A with EXAMPLE 169A.

## Example 169C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-((4-tetrahydro-2H-pyran-4-ylmorpholin-3-yl)methyl)amino)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and tetrahydropyran-4-one, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.77 (m, 1H), 8.57 (d, 1H), 8.05 (d, 1H), 7.84 (dd, 1H), 7.52 (m, 3H), 7.34 (m, 2H), 7.03 (m, 3H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.18 (d, 1H), 3.86 (m, 2H), 3.72 (m, 2H), 3.11 (m, 6H), 2.74 (m, 4H), 2.20 (m, 6H), 1.95 (m, 3H), 1.51 (m, 7H), 0.92 (s, 6H).

## Example 170

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-((4-cyclobutylmorpholin-3-yl)methyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and cyclobutanone. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.72 (s, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.84 (dd, 1H), 7.52 (m, 3H), 7.34 (m, 3H), 7.03 (m, 4H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.18 (d, 1H), 3.47 (m, 3H), 3.10 (m, 6H), 2.72 (m, 6H), 2.25 (m, 8H), 1.95 (m, 4H), 1.56 (m, 3H), 1.38 (m, 2H), 0.92 (s, 6H).

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## Example 171

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(4-tetrahydrofuran-3-ylmorpholin-3-yl)methyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 139C by replacing EXAMPLE 139B and oxetan-3-one with EXAMPLE 169B and 3-oxotetrahydrofuran, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.66 (s, 1H), 8.53 (d, 1H), 8.01 (d, 1H), 7.80 (d, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.98 (d, 1H), 6.66 (dd, 1H), 6.37 (d, 1H), 6.19 (d, 1H), 3.68 (m, 8H), 3.05 (m, 6H), 2.85 (m, 3H), 2.73 (s, 2H), 2.25 (m, 6H), 1.91 (m, 3H), 1.37 (m, 3H), 0.95 (m, 6H).

## Example 172

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-[2-fluoro-1-(fluoromethyl)ethyl]piperidin-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 163B for tert-butyl piperazine-1-carboxylate and 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.40 (br s, 1H), 8.57 (m, 2H), 8.03 (d, 1H), 7.78 (d, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 4.63 (d, 2H), 4.53 (d, 2H), 3.28 (m, 2H), 3.07 (m, 4H), 2.89 (m, 2H), 2.74 (m, 2H), 2.40 (m, 2H), 2.16 (m, 6H), 1.95 (s, 2H), 1.67 (m, 3H), 1.38 (t, 2H), 1.23 (m, 3H), 0.94 (s, 6H).

## Example 173

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 173A

4-((4-fluoropiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 126B for EXAMPLE 1A in EXAMPLE 1B.

## Example 173B

4-((1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

To EXAMPLE 173A (0.24 g) in methanol (3 mL) was added 3 Å molecular sieves (0.1 g), followed sequentially by acetic acid (0.31 mL), (1-ethoxycyclopropoxy)trimethylsilane (0.64 mL), and sodium cyanoborohydride (0.148 g). The reaction was heated under reflux overnight. After cooling, the reaction mixture was loaded onto a silica gel column. After drying, the column was eluted with 100:2:0.2 ethyl acetate/methanol/NH<sub>4</sub>OH to give the title compound.

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## Example 173C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropyl-4-fluoropiperidin-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 173B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.33 (s, 1H), 8.01 (m, 2H), 7.53 (d, 1H), 7.48-7.49 (m, 2H), 7.34-7.38 (m, 3H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.32 (d, 2H), 3.70-3.77 (m, 2H), 3.07 (s, 4H), 2.92 (s, 2H), 2.80 (s, 2H), 2.58 (s, 2H), 2.25 (s, 4H), 2.13-2.16 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H), 0.40-0.49 (m, 4H).

## Example 174

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A suspension of EXAMPLE 53A (120 mg), (4-methoxyphenyl)methanamine (31 mg) and Hunig's Base (0.159 mL) in dimethylsulfoxide (2 mL) was heated for 2 hours at 150° C. in a Biotage Initiator microwave reactor. The reaction mixture was diluted with methanol (2 mL) and purified by reverse phase HPLC (C8, 30%-100% CH<sub>3</sub>CN/water/0.1% trifluoroacetic acid). <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.32 (d, 1H), 9.17 (t, 1H), 8.43 (d, 1H), 8.28 (dd, 1H), 8.08 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.38 (d, 2H), 7.07 (d, 2H), 6.97-7.02 (m, 2H), 6.90 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.55 (d, 2H), 3.68 (s, 3H), 3.03-3.09 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10-2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 175

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[3-(trifluoromethoxy)benzyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-trifluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.38 (t, 1H), 9.31 (d, 1H), 8.42 (d, 1H), 8.28 (dd, 1H), 8.08 (d, 1H), 7.65 (ddd, 2H), 7.41-7.46 (m, 3H), 7.36-7.40 (m, 2H), 7.07 (d, 2H), 6.88 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (d, 1H), 4.73 (d, 2H), 3.02-3.08 (m, 4H), 2.77 (s, 2H), 2.22-2.28 (m, 2H), 2.09-2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 176

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-methoxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-methoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.27-9.32 (m, 2H), 8.42 (d, 1H), 8.26 (dd, 1H), 8.08 (d, 1H), 7.64-7.67 (m, 2H), 7.44 (d, 2H), 7.32 (t,



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1H), 7.14 (s, 1H), 7.04-7.09 (m, 3H), 6.88-6.94 (m, 2H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.48-6.50 (m, 1H), 4.64 (d, 2H), 3.68 (s, 3H), 3.03-3.09 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10-2.18 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 177**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (4-difluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.32 (d, 1H), 9.28 (t, 1H), 8.42 (d, 1H), 8.28 (dd, 1H), 8.07 (d, 1H), 7.66 (t, 1H), 7.64 (d, 1H), 7.58 (s, 1H), 7.44 (s, 2H), 7.26 (s, 1H), 7.25 (d, 1H), 7.07 (d, 2H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.64 (d, 2H), 3.03-3.10 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.11-2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

**Example 178**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[1,4-dioxaspiro[4.5]dec-8-ylamino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 1,4-dioxaspiro[4.5]dec-8-ylamine for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (br s, 1H), 8.55 (d, 1H), 8.26 (d, 1H), 8.04 (d, 1H), 7.81 (dd, 1H), 7.54-7.46 (m, 3H), 7.35 (d, 2H), 7.15 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.19 (d, 1H), 3.89 (s, 4H), 3.78 (m, 1H), 3.07 (br s, 4H), 2.78 (br s, 2H), 2.28-2.11 (m, 6H), 2.00-1.88 (m, 4H), 1.75-1.57 (m, 4H), 1.54-1.35 (m, 4H), 0.92 (s, 6H).

**Example 179**

Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 179A**

tert-butyl trans-4-acetamidocyclohexylcarbamate

Tert-butyl(trans)-4-aminocyclohexylcarbamate (1.500 g) and triethylamine (2.93 mL, 2.125 g) were added to dichloromethane and stirred until the tert-butyl(trans)-4-aminocyclohexylcarbamate had dissolved completely. Acetyl chloride (0.577 g) was added slowly, and the solution was stirred at room temperature for 16 hours. The solvent was removed, and the residue taken up in ethyl acetate, washed with pH 4 buffer, washed with brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum.

**Example 179B**

N-(trans-4-aminocyclohexyl)acetamide

The title compound was prepared by substituting EXAMPLE 179A for EXAMPLE 1A in EXAMPLE 1B.

**334****Example 179C**

Trans-N-[(4-{[4-(acetylamino)cyclohexyl]amino}-3-nitrophenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 179B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (br s, 1H), 8.55 (d, 1H), 8.20 (d, 1H), 8.04 (d, 1H), 7.82-7.76 (m, 2H), 7.53-7.46 (m, 3H), 7.35 (d, 2H), 7.16 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.57 (m, 2H), 3.07 (br s, 4H), 2.75 (br s, 2H), 2.28-2.10 (m, 6H), 2.03-1.94 (m, 4H), 1.83 (d, 2H), 1.80 (s, 3H), 1.55-1.24 (m, 6H), 0.92 (s, 6H).

**Example 180**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 180A**

(R)-tert-butyl  
1-(2,2-difluoroethyl)pyrrolidin-3-ylcarbamate

To a solution of (R)-tert-butyl pyrrolidin-3-ylcarbamate (500 mg) and 1,1-difluoro-2-iodoethane (618 mg) in N,N-dimethylformamide (6 mL) was added N-ethyl-N-isopropylpropan-2-amine (1.403 mL) and the mixture was stirred at 70° C. for 72 hours. The reaction mixture was concentrated and the crude product was purified on silica gel with methanol/dichloromethane.

**Example 180B**

(R)-1-(2,2-difluoroethyl)pyrrolidin-3-amine

To a solution of EXAMPLE 180A (525 mg) in a mixture of dichloromethane (3 mL) and methanol (4.0 mL) was added hydrogen chloride, 4M in dioxane (5.24 mL) and the reaction was stirred for 1.5 hours. The reaction was concentrated and the crude material was taken up in dichloromethane and the solvent evaporated, then taken up in ether and the solvent evaporated, and then dried on high vacuum.

**Example 180C**

(R)-4-(1-(2,2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 180B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 180D**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 180C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (m, 1H), 9.27 (d, 1H), 8.55 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.10 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.04-6.29 (m, 1H), 4.06 (m, 1H), 3.07 (m, 4H), 2.83-2.95 (m, 4H), 2.74-2.82 (m, 3H), 2.47 (m, 1H), 2.09-2.30 (m, 8H), 1.97 (s, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 181

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

## Example 181A

(S)-tert-butyl  
1-(2-fluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 1-fluoro-2-iodoethane for 1,1-difluoro-2-iodoethane and (S)-tert-butyl pyrrolidin-3-ylcarbamate for (R)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 180A.

## Example 181B

(S)-1-(2-fluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 181A for EXAMPLE 180A in EXAMPLE 180B.

## Example 181C

(S)-4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 181B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 181D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared by substituting EXAMPLE 181C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (m, 1H), 9.26 (d, 1H), 8.56 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.63-7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.60 (t, 1H), 4.51 (t, 1H), 4.05 (m, 1H), 3.07 (m, 4H), 2.84 (m, 1H), 2.66-2.79 (m,

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6H), 2.39 (q, 1H), 2.20-2.29 (m, 3H), 2.15 (m, 5H), 1.97 (s, 2H), 1.66 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 182

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

## Example 182A

(S)-tert-butyl  
1-(2,2-difluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylcarbamate for (R)-tert-butyl pyrrolidin-3-ylcarbamate in EXAMPLE 180A.

## Example 182B

(S)-1-(2,2-difluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 182A for EXAMPLE 180A in EXAMPLE 180B.

## Example 182C

(S)-4-(1-(2,2-difluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 182B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 182D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared by substituting EXAMPLE 182C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (m, 1H), 9.27 (d, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.64-7.68 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.04-6.29 (m, 1H), 4.06 (m, 1H), 3.07 (m, 4H), 2.83-2.95 (m, 4H), 2.74-2.82 (m, 3H), 2.47 (m, 1H), 2.09-2.30 (m, 8H), 1.97 (s, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 183

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 183A

(R)-tert-butyl  
1-(2-fluoroethyl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting 1-fluoro-2-iodoethane for 1,1-difluoro-2-iodoethane in EXAMPLE 180A.

## Example 183B

(R)-1-(2-fluoroethyl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 183A for EXAMPLE 180A in EXAMPLE 180B.

## Example 183C

(R)-4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 183B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 183D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(2-fluoroethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 183C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (m, 1H), 9.26 (d, 1H), 8.56 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.63-7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.83 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.60 (t, 1H), 4.50 (t, 1H), 4.04 (m, 1H), 3.07 (m, 4H), 2.84 (m, 1H), 2.66-2.79 (m, 6H), 2.39 (q, 1H), 2.19-2.28 (m, 3H), 2.14 (m, 5H), 1.97 (s, 2H), 1.66 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 184

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 184A

(S)-tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate

To a solution of (S)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (0.300 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.238 g). After stirring for 15 minutes,

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4-fluoro-3-nitrobenzenesulfonamide (0.295 g) was added and reaction stirred at room temperature. After 1 hour, the reaction was partitioned between water (25 mL) and dichloromethane (50 mL) and the reaction quenched with 1N aqueous HCl (5.96 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 12 g) eluting with a gradient of 0.2% to 2% methanol/dichloromethane over 30 minutes (flow=36 mL/minute) gave the title compound.

## Example 184B

(S)-3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methoxy)benzenesulfonamide

To (S)-tert-butyl 3-((2-nitro-4-sulfamoylphenoxy)methyl)pyrrolidine-1-carboxylate (0.433 g) was added hydrogen chloride (4.0M in dioxane, 1.0 mL). After stirring for 1 hour, the reaction was concentrated and partitioned between dichloromethane (50 mL) and saturated aqueous NaHCO<sub>3</sub> solution (50 mL). The aqueous layer was separated and concentrated. The residue was triturated with methanol (100 mL), filtered and concentrated and treated with sodium cyanoborohydride (0.068 g) and cyclobutanone (0.078 g) and stirred overnight. The reaction was partitioned between dichloromethane (50 mL) and water (25 mL) and saturated aqueous NaHCO<sub>3</sub> (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

## Example 184C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 184B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 11.45-11.01 (m, 1H), 8.30 (d, 1H), 7.98 (dd, 2H), 7.60-7.43 (m, 3H), 7.33 (t, 3H), 7.04 (d, 2H), 6.74-6.59 (m, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.49 (td, 2H), 4.33 (s, 1H), 4.13 (dd, 2H), 3.79 (s, 2H), 3.44 (dd, 2H), 3.07 (s, 4H), 2.74 (d, 6H), 2.19 (d, 6H), 1.98 (d, 2H), 1.74-1.52 (m, 1H), 1.39 (t, 2H), 0.92 (s, 6H).

## Example 185

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (4-hydroxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 11.67 (bs, 1H), 9.32 (d, 1H), 9.14 (s, 1H), 8.44 (d, 1H), 8.28 (dd, 1H), 8.09 (d, 1H), 7.65-7.68 (m, 2H), 7.44 (d, 2H), 7.37-7.41 (m, 2H), 7.19 (s, 2H), 7.07 (d, 2H), 6.93 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.54 (d, 2H), 3.02-3.09 (m, 4H), 2.77 (s, 2H), 2.22-2.29 (m, 2H), 2.10-2.17 (m, 4H), 1.97 (d, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

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## Example 186

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-hydroxybenzyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-hydroxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 11.67 (bs, 1H), 9.27-9.32 (m, 2H), 8.43 (d, 1H), 8.20 (dd, 1H), 8.08 (d, 1H), 7.66 (t, 2H), 7.44 (d, 2H), 7.33 (t, 1H), 7.25 (s, 1H), 7.13 (dd, 1H), 7.07 (d, 2H), 6.98 (d, 1H), 6.88 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.64 (d, 2H), 3.02-3.09 (m, 4H), 2.77 (s, 2H), 2.22-2.28 (m, 2H), 2.09-2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 187

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-difluoromethoxy)benzyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting (3-difluoromethoxyphenyl)methanamine for (4-methoxyphenyl)methanamine in EXAMPLE 174. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.34 (t, 1H), 9.30 (d, 1H), 8.42 (d, 1H), 8.26 (dd, 1H), 8.08 (d, 1H), 7.66 (ddd, 2H), 7.40-7.45 (m, 3H), 7.36 (t, 1H), 7.27-7.30 (m, 2H), 7.19 (d, 1H), 7.07 (d, 2H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.69 (d, 2H), 3.02-3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.09-2.16 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 188

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylcyclopentyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 188A

Cis-methyl 3-morpholinocyclopentanecarboxylate

The title compound was prepared by substituting methyl 3-oxocyclopentanecarboxylate for 4'-chlorobiphenyl-2-carboxaldehyde and morpholine for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 188B

Cis-3-morpholinocyclopentyl)methanol

The title compound was prepared by substituting EXAMPLE 188A for EXAMPLE 101C in EXAMPLE 101D.

## Example 188C

4-((Cis-3-morpholinocyclopentyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 188B for (1,4-dioxan-2-yl)methanol in EXAMPLE 12A.

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## Example 188D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(3-morpholin-4-ylcyclopentyl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 188C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.57 (s, 1H), 8.17 (m, 1H), 7.94 (m, 1H), 7.82 (m, 1H), 7.56 (d, 1H), 7.44 (t, 1H), 7.34 (m, 3H), 7.16 (m, 1H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.24 (d, 1H), 4.06 (m, 2H), 3.62 (m, 4H), 3.03 (m, 4H), 2.75 (s, 2H), 2.35 (m, 2H), 2.19 (m, 6H), 2.03 (m, 2H), 1.96 (s, 2H), 1.78 (m, 2H), 1.51 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H)

## Example 189

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 189A

Trans-(4-Methanesulfonylamino-cyclohexyl)-carbamic acid tert-butyl ester

The title compound was prepared by substituting methanesulfonyl chloride for acetyl chloride in EXAMPLE 179A.

## Example 189B

Trans-N-(4-Aminocyclohexyl)-methanesulfonamide

The title compound was prepared by substituting EXAMPLE 189A for EXAMPLE 1A in EXAMPLE 1B.

## Example 189C

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(methylsulfonyl)amino]cyclohexyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 189B for 1-acetylpiperidin-4-amine in EXAMPLE 53B. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (br s, 1H), 8.55 (d, 1H), 8.18 (d, 1H), 8.04 (d, 1H), 7.84 (d, 1H), 7.79 (dd, 1H), 7.56-7.47 (m, 3H), 7.34 (d, 2H), 7.16 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 3.56 (m, 1H), 3.17 (m, 1H), 3.07 (br s, 4H), 2.93 (s, 3H), 2.75 (br s, 2H), 2.28-2.10 (m, 6H), 2.05-1.90 (m, 6H), 1.55-1.32 (m, 6H), 0.92 (s, 6H).



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## Example 190

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 190A

4-(1-cyclopropylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

The title compound was prepared as described in EXAMPLE 17A by replacing (tetrahydropyran-4-yl)methylamine with 4-amino-1-cyclopropylpiperidine.

## Example 190B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-cyclopropylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 1G by replacing EXAMPLE 1E and EXAMPLE 1F with EXAMPLE 3J and EXAMPLE 190A, respectively. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.13 (d, 1H), 8.02 (d, 1H), 7.91 (m, 1H), 7.48 (m, 3H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (m, 2H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.64 (m, 1H), 3.13 (m, 5H), 2.73 (m, 5H), 2.22 (m, 6H), 1.92 (m, 5H), 1.70 (m, 1H), 1.41 (m, 5H), 0.94 (s, 6H), 0.41 (m, 4H).

## Example 191

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 191A

3-nitro-4-(piperidin-4-ylmethoxy)benzenesulfonamide

To a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (0.300 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.223 g). After stirring for 15 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.276 g) was added and reaction stirred at room temperature. After 1 hour the reaction was partitioned between water (25 mL) and dichloromethane (50 mL) and the reaction quenched with 1N aqueous HCl (5.57 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Treatment with HCl (4.0M in dioxane, 2 mL) and methanol (2 mL) for 1 hour, followed by concentration, trituration with dichloromethane and filtration gave the title compound.

## Example 191B

3-nitro-4-((1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a suspension of 3-nitro-4-(piperidin-4-ylmethoxy)benzenesulfonamide (0.100 g) and cyclobutanone (0.030 g) in

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methanol (1 mL) was added sodium cyanoborohydride (0.027 g). After stirring overnight, the reaction was quenched with saturated NaHCO<sub>3</sub> (5 mL) and extracted into dichloromethane (2×10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give the title compound.

## Example 191C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(1-oxetan-3-yl)piperidin-4-yl]methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 191B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 11.46-10.46 (m, 1H), 8.29 (s, 1H), 8.00 (d, 2H), 7.61-7.41 (m, 3H), 7.35 (d, 3H), 7.04 (d, 2H), 6.66 (d, 1H), 6.37 (s, 1H), 6.21 (s, 1H), 4.67-4.40 (m, 4H), 4.08 (d, 2H), 3.06 (s, 4H), 2.78 (s, 4H), 2.19 (m, 6H), 1.96 (s, 4H), 1.79 (m, 4H), 1.39 (s, 4H), 0.93 (s, 6H).

## Example 192

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 192A

4-((4-fluoro-1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

A mixture of EXAMPLE 173A (0.4 g), dihydro-2H-pyran-4(3H)-one (0.179 g), sodium cyanoborohydride (0.112 g), and acetic acid (0.5 mL) in tetrahydrofuran (3 mL) was stirred overnight. The solvents were removed under reduced pressure. The residue was purified with flash column chromatography on silica gel eluting with 100:5:0.5 ethyl acetate/methanol/NH<sub>4</sub>OH to give the desired product.

## Example 192B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydro-2H-pyran-4-yl)piperidin-4-yl]methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 192A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.25 (s, 1H), 7.96 (d, 1H), 7.93 (d, 1H), 7.57 (d, 1H), 7.45 (t, 1H), 7.34-7.37 (m, 3H), 7.26 (d, 1H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.34 (dd, 1H), 6.23 (d, 1H), 4.34 (d, 2H), 3.93 (dd, 2H),

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3.03 (s, 6H), 2.76 (s, 4H), 2.09-2.22 (m, 6H), 1.96 (s, 2H), 1.52-1.27 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 193

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 193A

4-((4-fluoro-1-(tetrahydrofuran-3-yl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting dihydrofuran-3(2H)-one for dihydro-2H-pyran-4(3H)-one in EXAMPLE 192A.

## Example 193B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-tetrahydrofuran-3-yl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 193A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.31 (s, 1H), 7.99-8.00 (m, 2H), 7.54 (d, 1H), 7.46-7.48 (m, 2H), 7.34-7.35 (m, 3H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.34 (d, 2H), 3.76-3.83 (m, 3H), 3.62-3.65 (m, 2H), 3.03 (s, 4H), 2.79 (s, 4H), 2.24 (s, 2H), 2.15 (s, 2H), 1.84-1.99 (m, 8H), 1.52-1.27 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 194

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 194A

4-((4-fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy)-3-nitrobenzenesulfonamide

A mixture of EXAMPLE 173A (0.4 g), methanesulfonyl chloride (0.113 g), and triethylamine (0.64 mL) in dichloromethane (5 mL) was stirred overnight. The reaction mixture was loaded onto a silica gel column and eluted with 100:1 ethyl acetate:methanol to give the clean product.

## Example 194B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluoro-1-(methylsulfonyl)piperidin-4-yl]methoxy}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 194A for EXAMPLE 11B in EXAMPLE 11D.

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<sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.37 (s, 1H), 8.06 (d, 1H), 8.02 (d, 1H), 7.49-7.53 (m, 3H), 7.42 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38-6.39 (m, 1H), 6.21 (d, 1H), 4.40 (d, 2H), 3.51-3.54 (m, 2H), 3.09 (s, 4H), 2.96-3.01 (m, 4H), 2.92 (s, 3H), 2.82 (s, 2H), 2.25-2.34 (m, 4H), 2.13-2.16 (m, 6H), 2.01-2.07 (m, 2H), 1.99 (s, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 195

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-([[(3R)-1-oxetan-3-ylpyrrolidin-3-yl]methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 195A

(R)-tert-butyl 3-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate for 1-acetylpiperidin-4-amine in EXAMPLE 53B.

## Example 195B

(S)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(pyrrolidin-3-ylmethylamino)phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 195A for EXAMPLE 1A in EXAMPLE 1B.

## Example 195C

(R)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methylamino)phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 195B for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) 11.67 (s, 1H), 8.81 (t, 1H), 8.55 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.50 (m, 3H), 7.35 (m, 2H), 7.04 (m, 3H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.57 (m, 2H), 4.48 (m, 2H), 3.68 (m, 2H), 3.30 (m, 2H), 3.06 (m, 4H), 2.74 (m, 3H), 2.56 (m, 3H), 2.44 (m, 1H), 2.18 (m, 5H), 1.95 (m, 3H), 1.58 (m, 1H), 1.36 (m, 2H), 0.94 (s, 6H).

## Example 196

Trans-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 196A

Trans-4-(4-(tert-butyl dimethylsilyloxy)cyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol

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with trans-(4-(tert-butyl dimethylsilyloxy)cyclohexyl)methanol (made according to the procedures in WO 2008/124878).

**Example 196B**

Trans-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(1r,4r)-4-(tert-butyl dimethylsilyloxy)cyclohexyl methoxy)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl) piperazin-1-yl)benzamide

The title compound was prepared as described in EXAMPLE 1G using EXAMPLE 196A in place of EXAMPLE 1F and EXAMPLE 3J in place of EXAMPLE 1E.

**Example 196C**

Trans-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-(4-([4-(4-hydroxycyclohexyl)methoxy]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 196B (150 mg) in dichloromethane (5 mL) and methanol (2 mL) was treated with 10% aqueous HCl (3 mL) for 1 hour and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a gradient of 40-60% acetonitrile in 0.1% trifluoroacetic acid water to give the title compound as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (30 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.27 (s, 1H), 8.34 (d, 1H), 7.95-8.08 (m, 2H), 7.47-7.55 (m, 3H), 7.32-7.40 (m, 3H), 7.01-7.07 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.54 (d, 1H), 3.96-4.06 (m, 2H), 3.10 (s, 4H), 2.84 (s, 2H), 2.05-2.39 (m, 6H), 1.96 (s, 2H), 1.46-1.93 (m, 5H), 1.39 (t, 2H), 0.98-1.29 (m, 4H), 0.92 (s, 6H)

**Example 197**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(4-(3-(dimethylamino)propoxy)benzyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 197A**

3-(4-(aminomethyl)phenoxy)-N,N-dimethylpropan-1-amine

4-(3-(Dimethylamino)propoxy)benzonitrile (300 mg) in methanol (20 mL) was treated with Raney nickel (wet, 1.5 g) under H<sub>2</sub> (30 psi) for 4 hour. The insoluble material was filtered off and the filtrate was concentrated to provide the title compound.

**Example 197B**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(4-(3-(dimethylamino)propoxy)benzyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using EXAMPLE 197A in place of

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EXAMPLE 120A. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.80 (t, 1H), 8.42 (d, 1H), 7.93 (d, 1H), 7.52-7.61 (m, 2H), 7.41-7.47 (m, 1H), 7.26-7.36 (m, 5H), 7.03-7.08 (m, 2H), 6.89 (d, 2H), 6.73 (d, 1H), 6.61 (dd, 1H), 6.31 (dd, 1H), 6.22 (d, 1H), 4.52 (d, 2H), 3.99 (t, 2H), 2.90-3.05 (m, 7H), 2.72 (s, 2H), 2.61 (s, 6H), 2.09-2.24 (m, 6H), 1.89-2.04 (m, 5H), 1.38 (t, 2H), 0.92 (s, 6H)

**Example 198**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(4-(2-morpholin-4-ylethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 198A**

(4-(2-morpholinoethoxy)phenyl)methanamine

The title compound was prepared as described in EXAMPLE 197A using 4-(2-morpholinoethoxy)benzonitrile in place of 4-(3-(dimethylamino)propoxy)benzonitrile.

**Example 198B**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(4-(2-morpholin-4-ylethoxy)benzyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 120B using EXAMPLE 198A in place of EXAMPLE 120A. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 9.00 (t, 1H), 8.56 (d, 1H), 8.02 (d, 1H), 7.72 (dd, 1H), 7.46-7.54 (m, 3H), 7.27-7.36 (m, 4H), 7.01-7.07 (m, 2H), 6.89-6.95 (m, 3H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.18 (d, 1H), 4.56 (d, 2H), 4.07 (t, 2H), 3.54-3.61 (m, 4H), 3.06 (s, 4H), 2.71-2.78 (m, 4H), 2.07-2.24 (m, 6H), 1.95 (s, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

**Example 199**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(4-((E)-4-hydroxy-1-adamantyl)methyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 199A**

4-(((E)-4-Hydroxy-adamantan-1-ylmethyl)-amino)-3-nitro-benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (0.5 g) and 5-(aminomethyl)adamantan-2-ol (0.6 g) in tetrahydrofuran (10 mL) were treated with triethylamine (1 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC, eluting 40-60% acetonitrile in 0.1 trifluoroacetic acid water to give two isomers, which were temporarily assigned as EXAMPLE 199A and EXAMPLE 199B, respectively.

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## Example 199B

4-(((Z)-4-Hydroxy-adamantan-1-ylmethyl)-amino)-  
3-nitro-benzenesulfonamide

4-Fluoro-3-nitrobenzenesulfonamide (0.5 g) and 5-(aminomethyl)adamantan-2-ol (0.6 g) in tetrahydrofuran (10 mL) were treated with triethylamine (1 mL) overnight. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC, eluting 40-60% acetonitrile in 0.1 trifluoroacetic acid water to give two isomers, which were temporarily assigned as EXAMPLE 199A and EXAMPLE 199B, respectively.

## Example 199C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-hydroxy-1-adamantyl)methyl]amino}-3-nitrophenyl sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 199A in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.40 (s, 1H), 8.55 (d, 1H), 8.50 (t, 1H), 8.03 (d, 1H), 7.77 (dd, 1H), 7.46-7.54 (m, 3H), 7.31-7.38 (m, 2H), 7.14 (d, 1H), 7.01-7.06 (m, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 4.61 (d, 1H), 3.63 (d, 1H), 3.02-3.16 (m, 6H), 2.75 (s, 2H), 2.17 (d, 6H), 2.04 (d, 2H), 1.95 (s, 2H), 1.76-1.88 (m, 3H), 1.49-1.61 (m, 6H), 1.38 (t, 2H), 1.29 (d, 2H), 0.92 (s, 6H).

## Example 200

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-hydroxy-1-adamantyl)methyl]amino}-3-nitrophenyl sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 199B in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.39 (s, 1H), 8.55 (d, 1H), 8.51 (t, 1H), 8.04 (d, 1H), 7.77 (dd, 1H), 7.46-7.55 (m, 3H), 7.31-7.37 (m, 2H), 7.14 (d, 1H), 7.01-7.06 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.61 (d, 1H), 3.61 (d, 1H), 3.08 (d, 6H), 2.75 (s, 2H), 2.17 (d, 6H), 1.79-1.99 (m, 7H), 1.55-1.69 (m, 4H), 1.49 (s, 2H), 1.38 (t, 2H), 1.22 (d, 2H), 0.92 (s, 6H).

## Example 201

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-yl-methoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 201A

4-((1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared as described in EXAMPLE 12A by replacing (1,4-dioxan-2-yl)methanol with (1S,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethanol.

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## Example 201B

N-({4-[(1S,4S)-bicyclo[2.2.1]hept-5-en-2-yl-methoxy]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 201A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.35 (d, 1H), 7.95-8.10 (m, 2H), 7.47-7.58 (m, 3H), 7.30-7.45 (m, 3H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (d, 1H), 5.92-6.23 (m, 3H), 3.65-4.39 (m, 3H), 3.00-3.22 (m, 4H), 2.76-2.98 (m, 4H), 2.28 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.71-1.91 (m, 1H), 1.33-1.47 (m, 3H), 1.20-1.32 (m, 2H), 0.92 (s, 6H), 0.50-0.66 (m, 1H).

## Example 202

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-methyl-5-oxopyrrolidin-3-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 82 (140 mg) was dissolved in dioxane (3.0 mL), and 4-amino-1-methylpyrrolidin-2-one hydrochloride (30 mg) and triethylamine (0.100 mL) were added. The reaction mixture was heated at 110° C. for 40 hours. The reaction was concentrated and the crude material was purified by preparative HPLC using a C18 column, 250x50 mm, 10μ, and eluting with a gradient of 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.74 (d, 1H), 8.37 (br d, 1H), 8.02 (d, 1H), 7.83 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.07 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.38 (m, 1H), 6.21 (d, 1H), 4.46 (m, 1H), 3.81 (dd, 1H), 3.38 (dd, 1H), 3.08 (br m, 4H), 2.82 (dd, 1H), 2.75 (s, 5H), 2.43 (dd, 1H), 2.21 (br m, 4H), 2.16 (br t, 2H), 1.95 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 203

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 203A

4-(((1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 201A (340 mg) in tetrahydrofuran (10 mL) and water (1 mL) was added N-methylmorpholine N-oxide (184 mg) and OsO<sub>4</sub> (2.5% in 2-methyl-2-propanol) (1.05 mL). The reaction mixture was stirred overnight and purified by reverse phase HPLC to provide two isomers, which were temporarily assigned as EXAMPLE 203A and EXAMPLE 203B, respectively.



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## Example 203B

4-(((1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]heptan-2-yl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 201A (340 mg) in tetrahydrofuran (10 mL) and water (1 mL) was added N-methylmorpholine N-oxide (184 mg) and OsO<sub>4</sub> (2.5% in 2-methyl-2-propanol) (1.05 mL). The reaction mixture was stirred overnight and purified by reverse phase HPLC to provide two isomers, which were temporarily assigned as EXAMPLE 203A and EXAMPLE 203B, respectively.

## Example 203C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1R,4R,5R,6S)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 203A in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.33 (s, 1H), 7.97-8.07 (m, 2H), 7.48-7.55 (m, 3H), 7.41 (d, 1H), 7.32-7.37 (m, 2H), 7.02-7.07 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.58 (dd, 2H), 4.07-4.19 (m, 2H), 3.82 (t, 1H), 3.51 (t, 1H), 3.09 (s, 4H), 2.81 (s, 2H), 2.09-2.34 (m, 8H), 2.04-2.09 (m, 2H), 1.93-2.01 (m, 3H), 1.62-1.77 (m, 2H), 1.39 (t, 2H), 1.11 (d, 1H), 0.92 (s, 6H), 0.67-0.76 (m, 1H).

## Example 204

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([1R,4R,5S,6R)-5,6-dihydroxybicyclo[2.2.1]hept-2-yl]methoxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 203B in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.33 (s, 1H), 7.98-8.07 (m, 2H), 7.49-7.54 (m, 3H), 7.41 (d, 1H), 7.32-7.36 (m, 2H), 7.02-7.07 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.58 (dd, 2H), 4.13 (dd, 2H), 3.82 (t, 1H), 3.51 (t, 1H), 3.09 (s, 4H), 2.81 (s, 2H), 2.09-2.35 (m, 8H), 2.07 (s, 2H), 1.93-2.02 (m, 3H), 1.61-1.80 (m, 2H), 1.39 (t, 2H), 1.11 (d, 1H), 0.92 (s, 6H), 0.66-0.78 (m, 1H).

## Example 205

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 205A

Methyl 1,4-dioxaspiro[4.5]decane-7-carboxylate

To a solution of trimethylsilyltrifluoromethanesulfonate (0.034 mL) in dry dichloromethane (5 mL) was added 1,2-bis(trimethylsiloxy)ethane (4.55 mL) followed by methyl 3-oxocyclohexanecarboxylate (2.9 g). The reaction mixture was stirred for 3 hours at -78° C. The reaction mixture was

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quenched with dry pyridine (0.5 mL), poured into saturated aqueous NaHCO<sub>3</sub>, and extracted with ether. The ether layer was dried over Na<sub>2</sub>CO<sub>3</sub>/Na<sub>2</sub>SO<sub>4</sub>. The reaction mixture was concentrated and purified by flash chromatography on silica with 5 to 30% ethyl acetate in hexanes to provide the title compound.

## Example 205B

1,4-dioxaspiro[4.5]decane-7-ylmethanol

The title compound was prepared by substituting EXAMPLE 205A for EXAMPLE 101C in EXAMPLE 101D.

## Example 205C

3-nitro-4-((3-oxocyclohexyl)methoxy)benzenesulfonamide

Into a 250 mL round-bottomed flask was added sodium hydride (0.5 g) in tetrahydrofuran (10 mL) and then 1,4-dioxaspiro[4.5]decane-7-ylmethanol (0.5 g) was added. After the mixture stirred at room temperature for 20 minutes, 4-fluoro-3-nitrobenzenesulfonamide (0.65 g) was added. The mixture was stirred at room temperature for overnight. Water (20 mL) was added slowly. The aqueous layer was extracted by dichloromethane (3×20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, and concentration of the filtrate, the residue was purified by reverse phase chromatography, eluting with 30-60% acetonitrile in water with 0.1% trifluoroacetic acid.

## Example 205D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(3-oxocyclohexyl)methoxy]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 205C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.22 (s, 1H), 7.96 (d, 1H), 7.87 (m, 1H), 7.55 (d, 1H), 7.45 (t, 1H), 7.35 (m, 3H), 7.20 (m, 1H), 7.04 (d, 2H), 6.64 (dd, 1H), 6.34 (m, 1H), 6.23 (d, 1H), 4.07 (d, 2H), 3.04 (m, 4H), 2.76 (s, 2H), 2.35 (m, 2H), 2.20 (m, 8H), 1.96 (m, 4H), 1.58 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 206

4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 206A

2-chloro-5,5-dimethylcyclohexa-1,3-dienecarbaldehyde

In a 250 mL round-bottomed flask was added N,N-dimethylformamide (3.5 mL) in dichloromethane (30 mL), and the mixture was cooled to -10° C. Phosphoryl trichloride (4 mL) was added dropwise, and the solution was warmed up to room temperature. 4,4-Dimethylcyclohex-2-enone (5.5 mL) was

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then added slowly, and the mixture was heated to reflux overnight. The reaction mixture was cooled and quenched with a 0° C. solution of sodium acetate (25 g in 50 mL water). The aqueous layer was extracted with diethyl ether (200 mL×3). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give the product.

## Example 206B

2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienecarbaldehyde

Into a 1 L round-bottomed flask was added EXAMPLE 206A (6.8 g), 4-chlorophenylboronic acid (6.5 g), and palladium (II) acetate (0.2 g) in water (100 mL) to give a suspension. Potassium carbonate (15 g) and tetrabutylammonium bromide (10 g) were added. After degassing, the mixture was stirred at 45° C. for 4 hours. After cooling and filtering through silica gel in a funnel, diethyl ether (4×200 mL) was used to extract the product. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and filtered. The filtrate was concentrated and purified by flash chromatography on silica with 0-10% ethyl acetate in hexanes to provide the title compound.

## Example 206C

Methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 206B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 206D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dienyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 206C for EXAMPLE 101E in EXAMPLE 101F.

## Example 206E

4-(4-([2-(4-chlorophenyl)-5,5-dimethylcyclohexa-1,3-dien-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 206D for EXAMPLE 3J and EXAMPLE 1F for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (400 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.61 (s, 1H), 8.49 (m, 2H), 7.99 (m, 1H), 7.72 (m, 1H), 7.53 (d, 1H), 7.41 (m, 4H), 7.12 (d, 2H), 6.99 (m, 1H), 6.66 (dd, 1H), 6.35 (m, 1H), 6.23 (d, 1H), 5.74 (d, 1H), 5.58 (d, 1H), 3.84 (m, 2H), 3.26 (m, 4H), 3.06 (m, 4H), 2.88 (s, 2H), 2.24 (m, 6H), 1.61 (m, 2H), 1.26 (m, 3H), 1.00 (s, 6H).

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## Example 207

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([3R]-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 207A

(R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-amine

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl azetidin-3-ylcarbamate in EXAMPLE 151A.

## Example 207B

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 207A for EXAMPLE 151A in EXAMPLE 151B.

## Example 207C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([3R]-1-[2-fluoro-1-(fluoromethyl)ethyl]pyrrolidin-3-yl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 207B for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.67 (s, 1H), 11.52-11.24 (m, 1H), 8.55 (d, 1H), 8.37 (d, 1H), 8.03 (d, 1H), 7.83 (dd, 1H), 7.57-7.45 (m, 3H), 7.34 (d, 2H), 7.06 (t, 3H), 6.67 (d, 1H), 6.38 (dd, 1H), 6.20 (d, 1H), 4.70 (d, 2H), 4.54 (d, 2H), 4.23 (s, 1H), 3.11-2.87 (m, 7H), 2.74 (dd, 4H), 2.35-2.13 (m, 7H), 1.95 (s, 2H), 1.70 (s, 1H), 1.39 (d, 2H), 0.92 (s, 6H).

## Example 208

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-([4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-5-(trifluoromethyl)pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 208A

2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-iodo-3-(trifluoromethyl)pyridine

A mixture of EXAMPLE 37C (0.537 g), 5-iodo-3-(trifluoromethyl)pyridin-2-ol (1.156 g), and triphenylphosphine (1.574 g) in tetrahydrofuran (20 mL) was cooled to 0° C. To this solution was added (E)-di-tert-butyl diazene-1,2-dicarboxylate (0.921 g). The reaction mixture was stirred overnight. The solvent was removed, and the residue was purified

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with column flash chromatography on silica gel eluting with 4:1 hexanes/ethyl acetate to give the desired product.

## Example 208B

6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

Example 207A (1.3 g) in tetrahydrofuran (10 mL) was cooled to  $-42^{\circ}\text{C}$ . with a cold bath of  $\text{CH}_3\text{CN}$ /dry ice. To this solution was added 2.0 M isopropylmagnesium chloride (1.6 mL) dropwise over 5 minutes. The reaction mixture was stirred for 30 minutes at  $-42^{\circ}\text{C}$ ., then allowed to warm to  $0^{\circ}\text{C}$ . over 10 minutes. The reaction mixture was cooled again to  $-42^{\circ}\text{C}$ ., and  $\text{SO}_2$  was bubbled through it for 10 minutes. The reaction mixture was stirred for another 30 minutes. To this solution was sulfuryl dichloride (0.433 g). On warming to room temperature, concentrated  $\text{NH}_4\text{OH}$  (10 mL) was added and the reaction mixture was stirred for another 2 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 3:1 hexanes/ethyl acetate to give the title compound.

## Example 208C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 208B for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.61 (s, 1H), 8.72 (s, 1H), 8.36 (s, 1H), 7.98 (d, 1H), 7.55 (d, 1H), 7.42-7.47 (m, 2H), 7.36 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.35 (s, 1H), 6.23 (s, 1H), 4.56 (d, 2H), 3.75-3.79 (m, 2H), 3.56-3.61 (m, 2H), 3.09 (s, 4H), 2.32-2.37 (m, 2H), 2.16 (s, 2H), 1.97-1.99 (m, 2H), 1.79-1.86 (m, 4H), 1.40 (t, 2H), 0.93 (s, 6H).

## Example 209

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[3-nitro-4-(([(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl)amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 209A

(S)-tert-butyl(1-(oxetan-3-yl)pyrrolidin-3-yl)methylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 209B

(S)-(1-(oxetan-3-yl)pyrrolidin-3-yl)methanamine

The title compound was prepared by substituting EXAMPLE 209A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

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## Example 209C

(S)-3-nitro-4-((1-(oxetan-3-yl)pyrrolidin-3-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and EXAMPLE 209B for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 209D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[3-nitro-4-(([(3S)-1-oxetan-3-ylpyrrolidin-3-yl]methyl)amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 209C for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.05 (s, 1H), 9.30 (d, 1H), 9.02 (t, 1H), 8.42 (d, 1H), 8.34 (dd, 1H), 8.10 (d, 1H), 7.67 (dd, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.75 (m, 1H), 6.52 (m, 2H), 4.82 (t, 1H), 4.75 (t, 1H), 4.67 (t, 2H), 3.57 (m, 1H), 3.24 (t, 2H), 3.07 (m, 4H), 2.75 (m, 3H), 2.57 (dd, 1H), 2.45 (s, 1H), 2.36 (t, 1H), 2.26 (s, 2H), 2.18 (m, 5H), 1.93 (m, 3H), 1.56 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 210

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 210A

(4-methoxycyclohexyl)methanol

The title compound was prepared by substituting 4-methoxycyclohexanecarboxylic acid for 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate in EXAMPLE 126A.

## Example 210B

Trans-5-chloro-6-((4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 210A for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 210C

Trans-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 210C for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.67 (s, 1H), 8.50 (s, 1H), 8.17 (s, 1H), 8.02 (d, 1H), 7.49-7.54 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.39 (s, 1H), 6.21

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(s, 1H), 4.20 (d, 2H), 3.23 (s, 3H), 3.06-3.09 (m, 4H), 2.15-2.37 (m, 4H), 1.96-2.03 (m, 4H), 1.74-1.84 (m, 2H), 1.40 (t, 2H), 1.04-1.13 (m, 4H), 0.93 (s, 6H).

## Example 211

Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 211A

Cis-5-chloro-6-((4-methoxycyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was isolated as a by-product in the synthesis of EXAMPLE 210B.

## Example 211B

Cis-N-({5-chloro-6-[(4-methoxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 211A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.03 (d, 1H), 7.49-7.54 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (s, 1H), 6.21 (s, 1H), 4.21 (d, 2H), 3.20 (s, 3H), 3.06 (s, 4H), 2.15-2.37 (m, 4H), 1.96 (s, 2H), 1.80-1.84 (m, 2H), 1.50-1.54 (m, 2H), 1.34-1.44 (m, 6H), 0.93 (s, 6H).

## Example 212

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 212A

(S)-tert-butyl 1-(oxetan-3-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (S)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 212B

(S)-1-(oxetan-3-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 212A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

## Example 212C

(S)-3-nitro-4-(1-(oxetan-3-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzene-

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sulfonamide and EXAMPLE 212B for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 212D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3S)-1-oxetan-3-ylpyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 212C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.58 (d, 1H), 8.42 (d, 1H), 8.37 (dd, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.67 (m, 4H), 4.09 (m, 1H), 3.59 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.69 (m, 2H), 2.62 (dd, 1H), 2.28 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.68 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 213

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 213A

4-((4-(2-(2-methoxyethoxy)ethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(2'-methoxyethoxy)ethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 213B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-[2-(2-methoxyethoxy)ethyl]morpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 213A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.98 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.96-3.86 (m, 2H), 3.72 (dd, 1H), 3.67-3.61 (m, 4H), 3.51 (t, 2H), 3.48-3.38 (m, 2H), 3.28 (s, 3H), 3.07 (m, 4H), 2.95 (d, 1H), 2.77 (s, 2H), 2.70 (m, 1H), 2.60 (t, 2H), 2.30-2.05 (m, 8H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).



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## Example 214

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(cyanomethyl)morpholin-2-yl]methyl}amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 214A

4-((4-(cyanomethyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

## Example 214B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(cyanomethyl)morpholin-2-yl]methyl}amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 214A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.93 (m, 1H), 3.87 (d, 1H), 3.77 (s, 2H), 3.65 (dt, 1H), 3.51-3.40 (m, 2H), 3.07 (m, 4H), 2.87 (d, 1H), 2.77 (s, 2H), 2.60 (d, 1H), 2.50 (m, 1H), 2.38 (t, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 215

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 215A

4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-dimethylaminoacetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

## Example 215B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino]-3-nitrophenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 215A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd,

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1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 216

(2-{[4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl]amino]methyl}morpholin-4-yl)acetic acid

## Example 216A

tert-butyl 2-(2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholino)acetate

The title compound was prepared by substituting tert-butyl 2-bromoacetate for methyl iodide in EXAMPLE 134B.

## Example 216B

tert-butyl 2-(2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)methyl)morpholino)acetate

The title compound was prepared by substituting EXAMPLE 216A for EXAMPLE 130C in EXAMPLE 130D.

## Example 216C

(2-{[4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl]amino]methyl}morpholin-4-yl)acetic acid

The title compound was prepared by treating EXAMPLE 216B with 50% trifluoroacetic acid in dichloromethane. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.97 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.30 (dd, 1H), 8.12 (d, 1H), 7.69 (t, 1H), 7.64 (d, 1H), 7.43 (d, 2H), 7.08 (d, 2H), 6.88 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 6.47 (m, 1H), 4.05-4.00 (m, 1H), 3.91 (d, 1H), 3.79 (dt, 1H), 3.50 (s, 2H), 3.45 (m, 2H), 3.13 (d, 1H), 3.07 (m, 4H), 2.88 (d, 1H), 2.78 (s, 2H), 2.57 (dt, 1H), 2.43 (t, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 217

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-{[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino]phenyl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 217A

The title compound was prepared by substituting EXAMPLE 134A for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

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## Example 217B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 217A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.64 (m, 4H), 3.93 (m, 1H), 3.89 (d, 1H), 3.68 (dt, 1H), 3.53-3.35 (m, 3H), 3.07 (m, 4H), 2.77 (s, 2H), 2.72 (d, 1H), 2.44 (d, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.85 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 218

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 218A

4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 134A for EXAMPLE 173A in EXAMPLE 173B.

## Example 218B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(cyclopropylmorpholin-2-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 218A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

## Example 219

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 219A

5-(methylthio)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 36B (0.1 g) and sodium methanethiolate (0.04 g) in N,N-dimethylformamide (2 mL) was

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heated at 80° C. overnight. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

## Example 219B

5-(methylsulfonyl)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 219A (0.15 g) and 75% meta-chloroperoxybenzoic acid (0.217 g) in chloroform (4 mL) was stirred at room temperature. The reaction mixture was stirred overnight. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

## Example 219C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(5-(methylsulfonyl)-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 219B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.81 (s, 1H), 8.55 (d, 1H), 8.01 (d, 1H), 7.55 (d, 1H), 7.49-7.50 (m, 2H), 7.37 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.36 (d, 2H), 3.88 (dd, 2H), 3.13 (s, 4H), 2.95 (s, 2H), 2.36-2.38 (m, 2H), 2.03-2.16 (m, 4H), 1.97 (s, 3H), 1.66-1.69 (m, 2H), 1.38-1.402 (m, 4H), 0.93 (s, 6H).

## Example 220

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[4-(fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 220A

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethylsulfonyl)benzenesulfonamide

To a solution of EXAMPLE 37C (0.500 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.596 g). Additional tetrahydrofuran (25 mL) was added and the mixture stirred for 30 minutes, then 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (1.145 g) was added as a solution in tetrahydrofuran (5 mL). After stirring for 2 hours, the reaction

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mixture was partitioned between 1N aqueous HCl (50 mL) and dichloromethane (200 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting solid was chromatographed over silica gel (Reveleris 80 g) eluting with a gradient of 0.5% to 7.5% methanol/dichloromethane over 30 minutes (flow=40 mL/min) to provide the title compound.

**Example 220B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 220A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.42 (s, 1H), 8.35-8.22 (m, 1H), 8.01 (s, 1H), 7.49 (d, 4H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (s, 1H), 6.38 (s, 1H), 6.21 (s, 1H), 4.42 (d, 2H), 3.76 (s, 2H), 3.59 (s, 2H), 3.10 (s, 6H), 2.15 (s, 6H), 2.02-1.74 (m, 6H), 1.40 (s, 2H), 0.93 (s, 6H).

**Example 221**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 221A**

4-((4-methyltetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting (4-methyltetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

**Example 221B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methyltetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 221A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.36 (s, 1H), 8.04-8.06 (m, 2H), 7.50-7.53 (m, 3H), 7.41 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.00 (s, 2H), 3.63-3.67 (m, 2H), 3.53-3.58 (m, 2H), 3.09 (s, 4H), 2.82 (s, 2H), 2.27 (s, 2H), 2.15 (s, 2H), 1.58-1.63 (m, 2H), 1.39 (t, 2H), 1.30-1.34 (m, 2H), 1.09 (s, 3H), 0.92 (s, 6H).

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ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate

**Example 222A**

ethyl 4-(2-nitro-4-sulfamoylphenyl)piperazine-1-carboxylate

The title compound was prepared by substituting ethyl piperazine-1-carboxylate for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 222B**

ethyl 4-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl]-2-nitrophenyl)piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 222A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.52 (br. s, 1H), 8.08 (d, 1H), 7.89 (d, 1H), 7.59 (m, 2H), 7.43 (t, 1H), 7.35 (d, 2H), 7.23 (d, 1H), 7.05 (d, 2H), 6.94 (d, 1H), 6.63 (dd, 1H), 6.29 (m, 2H), 4.07 (q, 2H), 3.47 (m, 4H), 3.17 (d, 2H), 3.00 (m, 8H), 2.73 (s, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.39 (t, 2H), 1.20 (t, 3H), 0.93 (s, 6H).

**Example 223**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 223A**

The title compound was prepared by substituting 4-(piperidin-4-yl)morpholine for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 223B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-morpholin-4-yl)piperidin-1-yl]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 223A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.53 (br. s, 1H), 8.05 (d, 1H), 7.91 (d, 1H), 7.58 (m, 2H), 7.43 (t, 1H), 7.35 (d, 2H), 7.26 (d, 1H), 7.05 (d, 2H), 6.91 (d, 1H), 6.62 (dd, 1H), 6.29 (m, 2H), 5.76 (s, 1H), 3.57 (m, 4H), 3.20 (m, 2H), 3.01 (m, 4H), 2.80 (t, 2H), 2.73 (s, 2H), 2.47 (m, 4H), 2.32 (m, 1H), 2.18 (m, 6H), 1.96 (m, 3H), 1.82 (m, 2H), 1.44 (m, 4H), 0.93 (s, 6H).

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## Example 224

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 224A

(R)-tert-butyl 1-(oxetan-3-yl)pyrrolidin-3-ylcarbamate

The title compound was prepared by substituting (R)-tert-butyl pyrrolidin-3-ylcarbamate for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 224B

(R)-1-(oxetan-3-yl)pyrrolidin-3-amine

The title compound was prepared by substituting EXAMPLE 224A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

## Example 224C

(R)-3-nitro-4-(1-(oxetan-3-yl)pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-nitrobenzenesulfonamide for 4-chloro-3-nitrobenzenesulfonamide and EXAMPLE 224B for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

## Example 224D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(3R)-1-(oxetan-3-yl)pyrrolidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 224C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.26 (d, 1H), 8.57 (d, 1H), 8.42 (d, 1H), 8.36 (dd, 1H), 8.09 (d, 1H), 7.66 (m, 1H), 7.64 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.67 (m, 4H), 3.58 (m, 1H), 3.07 (m, 4H), 2.77 (m, 2H), 2.68 (m, 2H), 2.61 (m, 1H), 2.28 (m, 4H), 2.14 (m, 4H), 1.97 (m, 2H), 1.67 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 225

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-{(trifluoromethyl)sulfonyl}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 225A

(R)-4-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

To EXAMPLE 207A (0.217 g) and 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (0.281 g) in tetrahydrofu-

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ran (5 mL) was added diisopropylethylamine (0.559 mL) and the reaction was allowed to stir at room temperature for 1 hour and was then heated to 50° C. for 1 hour. The reaction was concentrated, the residue was loaded onto silica gel (Reveleris 40 g) and eluted with a gradient of 0.75% methanol/dichloromethane to 7.5% methanol/dichloromethane to provide the title compound.

## Example 225B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}-3-{(trifluoromethyl)sulfonyl}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 225A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.52-11.23 (m, 1H), 8.17 (d, 1H), 8.04 (d, 1H), 7.95 (d, 1H), 7.54 (d, 1H), 7.53-7.50 (m, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.10-6.97 (m, 4H), 6.67 (d, 1H), 6.40 (dd, 1H), 6.18 (d, 1H), 4.60 (dd, 4H), 4.20 (s, 1H), 3.11-2.63 (m, 12H), 2.19 (d, 6H), 1.95 (s, 2H), 1.58 (s, 1H), 1.40 (d, 2H), 0.92 (s, 6H).

## Example 226

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 226A

tert-butyl 4-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)piperidine-1-carboxylate

To a solution of EXAMPLE 82 (800 mg) and tert-butyl 4-aminopiperidine-1-carboxylate (203 mg) in dioxane (10 mL) was added Hunig's Base (1 mL). The mixture was stirred at 120° C. overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of solvent, the residue was loaded on a silica gel cartridge and eluted with 3% methanol in dichloromethane to give the title compound.

## Example 226B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperidin-4-ylamino)phenyl)sulfonyl)benzamide

To a solution of EXAMPLE 226A (902 mg) in dichloromethane (10 mL) was added trifluoroacetic acid (5 mL). The mixture was stirred at room temperature for 3 hours. The mixture was concentrated under vacuum and co-concentrated with dichloromethane twice to afford the crude product which was used in the next step without further purification.



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## Example 226C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1-isopropylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 226B (79 mg) in tetrahydrofuran (3 mL) and acetic acid (1 mL) was added acetone (54 mg) and MP-cyanoborohydride (150 mg, 2.25 mmol/g). The mixture was stirred overnight. The mixture was filtered. The filtrate was concentrated and the residue was loaded on a silica gel cartridge and eluted with 5 to 10% 7N NH<sub>3</sub> in methanol in dichloromethane to provide the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 12.09 (s, 1H), 8.34 (m, 1H), 7.93 (m, 2H), 7.66 (m, 4H), 7.35 (d, 2H), 7.06 (d, 2H), 6.89 (m, 1H), 6.74 (dd, 1H), 6.59 (dd, 1H), 6.50 (d, 1H), 3.11 (m, 6H), 2.73 (m, 4H), 2.26 (m, 9H), 1.97 (s, 3H), 1.40 (t, 2H), 1.23 (s, 8H), 0.94 (s, 6H).

## Example 227

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 227A

## 1-tert-butylpiperidin-4-amine

To a solution of 1-tert-butylpiperidin-4-one (5.0 g) in methanol (100 mL) and water (10 mL) was added ammonium formate (20.3 g) and 0.5 g of Pd/C (10%). The mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated under vacuum and the residue was diluted with ethyl acetate (500 mL) and washed with water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub> and filtration, the solvent was evaporated under vacuum to provide the title compound.

## Example 227B

4-(1-tert-butylpiperidin-4-ylamino)-3-nitrobenzenesulfonamide

To a mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.2 g) and EXAMPLE 227A (1.56 g) in tetrahydrofuran (20 mL) was added Hunig's Base (6 mL). The mixture was stirred for 3 days. The mixture was diluted with ethyl acetate (300 mL) and water (100 mL) and stirred until the solid disappeared into the solution. The layers were separated and the organic phase was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The combined aqueous layers were extracted again with ethyl acetate and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was evaporated to provide the title compound.

## Example 227C

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-nitrophenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 227B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.51 (s, 1H), 8.43 (d, 1H), 8.04 (m, 1H), 7.93 (d, 1H), 7.72 (m, 1H), 7.56 (dd, 1H), 7.42 (m, 1H), 7.34 (m, 3H), 7.05 (d, 2H), 6.93 (dd, 1H), 6.62 (dd, 1H), 6.28 (m, 1H), 3.04 (m, 6H), 2.73 (s, 3H), 2.25 (m, 9H), 1.95 (s, 2H), 1.68 (m, 2H), 1.32 (m, 9H), 0.93 (s, 6H).

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## Example 228

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-(2-methoxyethyl)piperidin-3-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 228A

tert-butyl 3-((2-nitro-4-sulfamoylphenylamino)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)piperidine-1-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 228B

3-nitro-4-(piperidin-3-ylmethylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 228A for EXAMPLE 113A in EXAMPLE 134A.

## Example 228C

4-((1-(2-methoxyethyl)piperidin-3-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 228B for EXAMPLE 134A and 2-methoxyethyl bromide for methyl iodide in EXAMPLE 134B.

## Example 228D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-([1-(2-methoxyethyl)piperidin-3-yl]methyl)amino}-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 228C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>, 90° C.) δ 12.40 (s, 1H), 8.52 (s, 1H), 8.43 (s, 1H), 8.20 (m, 2H), 7.95 (bs, 1H), 7.80 (s, 1H), 7.46 (d, 1H), 7.36 (d, 2H), 7.07 (d, 2H), 7.05 (s, 1H), 6.75 (d, 1H), 6.59 (s, 1H), 6.47 (s, 1H), 3.65-3.50 (m, 5H), 3.20 (s, 3H), 3.04 (m, 5H), 2.81 (s, 3H), 2.74 (m, 1H), 2.24 (m, 7H), 2.06 (s, 2H), 2.00 (s, 2H), 1.75 (m, 1H), 1.57 (m, 2H), 1.42 (t, 2H), 1.15 (m, 1H), 0.95 (s, 6H).

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## Example 229

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[1-(cyanomethyl)piperidin-3-yl]methyl}amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 229A

4-((1-(cyanomethyl)piperidin-3-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 228B for EXAMPLE 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

## Example 229B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[1-(cyanomethyl)piperidin-3-yl]methyl}amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 229A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.03 (s, 1H), 8.42 (s, 1H), 8.30 (d, 1H), 8.10 (d, 1H), 7.68 (m, 2H), 7.44 (d, 2H), 7.08 (m, 3H), 6.99 (d, 1H), 6.75 (d, 1H), 6.51 (m, 2H), 3.78 (m, 2H), 3.43 (d, 1H), 3.13 (m, 1H), 3.04 (m, 4H), 2.76 (s, 2H), 2.71-2.65 (m, 3H), 2.52 (m, 1H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.84 (m, 1H), 1.68 (m, 1H), 1.50 (m, 2H), 1.39 (t, 2H), 1.07-0.99 (m, 1H), 0.93 (s, 6H).

## Example 230

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-fluoro-1-methylpiperidin-4-yl]methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 230A

4-((4-fluoro-1-methylpiperidin-4-yl)methoxy)-3-(trifluoromethylsulfonyl)benzenesulfonamide

To a solution of (4-fluoro-1-methylpiperidin-4-yl)methanol (0.315 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.342 g). After stirring for 15 minutes, 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (0.658 g) was added as a solution in tetrahydrofuran (2 mL) followed by additional tetrahydrofuran (5 mL). After stirring for 1 hour, the reaction was poured in dichloromethane (50 mL) and water (25 mL) and the pH of the water layer was adjusted to 8. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was chromatographed over silica gel (Reveleris 40 g) eluting with a gradient of 1.0% to 10% 7N NH<sub>3</sub> in methanol/dichloromethane over 20 minutes then maintaining 10% 7N NH<sub>3</sub> in methanol/dichloromethane for 5 minutes (flow=30 mL/min) to provide the title compound.

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## Example 230B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-fluoro-1-methylpiperidin-4-yl]methoxy]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 230A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63-11.57 (m, 1H), 8.40-8.36 (m, 1H), 8.28-8.17 (m, 1H), 7.97 (s, 1H), 7.53 (d, 1H), 7.50-7.32 (m, 5H), 7.05 (d, 1H), 7.05 (d, 1H), 6.68-6.61 (m, 1H), 6.35 (s, 1H), 6.22 (s, 1H), 4.55-4.40 (m, 2H), 3.06 (s, 8H), 2.79 (s, 4H), 2.06 (d, 13H), 1.39 (s, 2H), 0.93 (s, 6H).

## Example 231

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 231A

(R)-5-chloro-6-(1-(1,3-difluoropropan-2-yl)pyrrolidin-3-ylamino)pyridine-3-sulfonamide

To EXAMPLE 207A (0.051 g) and EXAMPLE 40A (0.049 g) in dioxane (5 mL) was added diisopropylethylamine (0.131 mL) and the reaction was heated to 75° C. for 1 hour then 85° C. for 2 days. The reaction was concentrated, loaded onto silica gel (Reveleris 12 g) and eluted with a gradient of 0.75% methanol/dichloromethane to 7.5% methanol/dichloromethane to provide the title compound.

## Example 231B

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]amino}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 231A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.44-11.11 (m, 1H), 8.44 (d, 1H), 8.07 (d, 1H), 7.90 (d, 1H), 7.61 (d, 1H), 7.52 (dd, 2H), 7.34 (d, 2H), 7.19 (s, 1H), 7.04 (d, 2H), 6.67 (d, 1H), 6.42 (dd, 1H), 6.16 (s, 1H), 4.77-4.39 (m, 5H), 3.19-2.63 (m, 11H), 2.19 (s, 7H), 1.91 (d, 3H), 1.38 (s, 2H), 0.92 (s, 6H).

## Example 232

tert-butyl 4-[(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy]benzoyl}sulfamoyl]-2-nitrophenyl)amino]piperazine-1-carboxylate

## Example 232A

tert-butyl 4-nitrosopiperazine-1-carboxylate

In a 500 mL round-bottomed flask, 6N aqueous HCl (30 mL) was cooled to -10° C., and tert-butyl piperazine-1-carboxylate

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boxylate (10 g) was added. Sodium nitrite (4.5 g) dissolved in 35 ml water was added slowly. NaOH (10 g in 20 mL water) was used to neutralize the solution. Dichloromethane (3x50 mL) was used to extract the product. After drying over Na<sub>2</sub>SO<sub>4</sub> and filtration, the solution was concentrated. The crude product was added to a silica gel column (Analogix, SF65-400 g,) and purified by eluting with 0-30% ethyl acetate in hexane.

## Example 232B

## tert-butyl 4-aminopiperazine-1-carboxylate

In a 100 mL round-bottomed flask was added EXAMPLE 232A (0.15 g) and zinc (1 g) in water/methanol (1:1, 10 mL) to give a suspension. The mixture was cooled to 0° C. 12N Aqueous HCl (2 ml) was added slowly, and the mixture was stirred at 0° C. for 30 minutes. 2N Aqueous NaOH solution was used to adjust the mixture to basic pH. The mixture was filtered, and extracted with ether (3x30 mL). After drying over Na<sub>2</sub>SO<sub>4</sub>, filtration, and concentration, the crude product was added to a silica gel column (Analogix, SF15-12 g,) and purified by eluting with 0-25% ethyl acetate in hexane.

## Example 232C

## tert-butyl 4-(2-nitro-4-sulfamoylphenylamino)piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 232B for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 232D

## tert-butyl 4-[(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl-2-nitrophenylamino]piperazine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 232C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.47 (br. s, 1H), 8.86 (s, 1H), 8.34 (d, 1H), 7.90 (d, 1H), 7.59 (m, 2H), 7.36 (m, 4H), 7.23 (m, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.27 (m, 2H), 2.99 (m, 5H), 2.76 (m, 6H), 2.19 (m, 6H), 1.96 (s, 2H), 1.41 (m, 11H), 1.24 (m, 4H), 0.93 (s, 6H).

## Example 233

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-(3-(pentafluorolambda-6-sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 233A

## 2-(5-bromo-2-nitrophenyl)sulfur pentafluoride

To a solution of 3-bromophenylsulfur pentafluoride (2.18 g) in concentrated H<sub>2</sub>SO<sub>4</sub> (5 mL) was added KNO<sub>3</sub> (780 mg). The mixture was stirred overnight. The mixture was diluted with diethyl ether (100 mL) and washed with water and brine.

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After drying over Na<sub>2</sub>SO<sub>4</sub> and filtration, the solvent was evaporated under vacuum to provide the title compound.

## Example 233B

## 2-(5-bromo-2-aminophenyl)sulfur pentafluoride

EXAMPLE 233A (6.4 g) and tetrahydrofuran (300 mL) were added to Ra—Ni, (12.80 g) in a 50 mL pressure bottle and the mixture stirred for 2 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and the filtrate was concentrated under vacuum to provide the title compound.

## Example 233C

## 4-bromo-2-pentafluorosulfanyl-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

To a solution of EXAMPLE 233B (4.4 g) in methanol (50 mL) was added tetrahydro-2H-pyran-4-carbaldehyde (1.68 g) and decaborane (1.1 g). The mixture was stirred and monitored by thin layer chromatography. More tetrahydro-2H-pyran-4-carbaldehyde (500 mg) was added to the stirring mixture to drive the reaction to completion. The reaction mixture was concentrated under vacuum and ethyl acetate (500 mL) and brine (200 mL) were added. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent and flash chromatography (20% ethyl acetate in hexane) gave the title compound.

## Example 233D

## 4-thioacetoxyl-2-pentafluorosulfanyl-N-(tetrahydro-2H-pyran-4-ylmethyl)aniline

To a solution of EXAMPLE 233C (456 mg) and potassium ethanethioate (197 mg) in dioxane (4 mL) was added tris (dibenzylideneacetone)dipalladium(0) (27 mg) and xantphos (33 mg) followed by N,N-diisopropylethylamine (0.5 mL). The mixture was purged with argon, sealed and stirred under microwave irradiation for 60 minutes at 120° C. The mixture was dissolved in ethyl acetate (300 mL) and water (100 mL). The organic phase was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent followed by flash chromatography (20% ethyl acetate in hexane) provided the title compound.

## Example 233E

## 3-pentafluorosulfanyl-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenylsulfonamide

N-chlorosuccinimide (527 mg) was added to a mixture of 2N aqueous HCl (1.5 mL) and acetonitrile (12 mL) and then cooled to 0° C. A solution of EXAMPLE 233D (386 mg) in acetonitrile (3 mL) was added to the mixture which was then stirred at 0° C. for 2 hours, and then diluted with ethyl acetate (300 mL) and washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of solvent, the residue was dissolved in isopropyl alcohol (20 mL) and cooled to 0° C. with stirring. Then, ammonium hydroxide (conc. 10 mL) was added to mixture. After stirring for 2 hours, the mixture was concentrated under vacuum and the residue was added to ethyl acetate (400 mL) and water (150 mL). The organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration

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and evaporation of solvent, the residue was purified by flash column (20% ethyl acetate in dichloromethane) to provide the title compound.

## Example 233F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-(pentafluoro-lambda-6-sulfanyl)-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 233E for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.33 (m, 1H), 8.12 (m, 2H), 7.72 (d, 1H), 7.54 (m, 3H), 7.33 (m, 2H), 7.02 (m, 3H), 6.67 (m, 2H), 6.42 (m, 1H), 6.16 (d, 1H), 3.82 (m, 2H), 3.21 (m, 4H), 3.05 (m, 4H), 2.73 (s, 2H), 2.21 (m, 8H), 1.97 (m, 3H), 1.29 (m, 4H), 0.92 (s, 6H).

## Example 234

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 234A

4-vinyltetrahydro-2H-pyran-4-ol

Dihydro-2H-pyran-4(3H)-one (8.01 g) in anhydrous ethyl ether (50 mL) was treated with 1.0 M vinylmagnesium bromide (104 mL) over 20 minutes at 0° C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH<sub>4</sub>Cl, and the organic layer was separated. The aqueous layer was extracted with additional ethyl ether three times. The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 20% ethyl acetate in hexanes to provide the title compound.

## Example 234B

4-methoxy-4-vinyltetrahydro-2H-pyran

To a solution of EXAMPLE 234A (9.4 g) in tetrahydrofuran (150 mL) was added 60% sodium hydride (5.28 g) at 0° C. portionwise. After the addition was complete, the solution was heated under reflux for three hours. After cooling, to this suspension was added dimethyl sulfate (8.41 mL) slowly. The solution was heated under reflux overnight, cooled to room temperature, and hydrolyzed with cool saturated aqueous NH<sub>4</sub>Cl. After extraction with diethyl ether several times, the combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatograph on silica gel using 1-10% ethyl acetate in hexanes to provide the title compound.

## Example 234C

4-methoxytetrahydro-2H-pyran-4-carbaldehyde

EXAMPLE 234B (4.3 g) in tetrahydrofuran (200 mL) and water (67 mL) was treated with 4% osmium tetroxide in water

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(9.24 mL). To this solution was added potassium periodate (13.91 g) portionwise over 2 hours. The solution was stirred overnight at room temperature. Water was added to the mixture followed by repeat extractions with diethyl ether. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 5-20% ethyl acetate in hexanes to provide the title compound.

## Example 234D

(4-methoxytetrahydro-2H-pyran-4-yl)methanol

EXAMPLE 234C (1.8 g) in 2-propanol (28 mL) and water (7 mL) was cooled to 0° C. To this solution was added sodium borohydride (0.709 g). The solution was stirred and allowed to warm to room temperature over 3 hours. The reaction was quenched with acetone, and stirred for another 1 hour. The clear liquid was separated from solid by decanting. Additional ethyl acetate was used to wash the solid, and was the mixture was decanted. The combined organic solutions were concentrated. The residue was purified by flash chromatography on silica gel eluting 1:1 ethyl acetate:hexane to provide the title compound.

## Example 234E

4-((4-methoxytetrahydro-2H-pyran-4-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 234D for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 234F

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-methoxytetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 234E for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.36 (s, 1H), 8.04-8.07 (m, 2H), 7.50-7.53 (m, 3H), 7.45 (d, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.21 (s, 2H), 3.65-3.67 (m, 2H), 3.53-3.56 (m, 2H), 3.19 (s, 3H), 3.10 (s, 4H), 2.86 (s, 2H), 2.30 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.61-1.74 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 235

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 235A

(R)-tert-butyl 3-(2-nitro-4-sulfamoylphenoxy)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.



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(R)-tert-butyl 3-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenoxy)pyrrolidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 235A for EXAMPLE 1F in EXAMPLE 1G.

**Example 235C**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 235B (0.230 g) in dichloromethane (3 mL) was added trifluoroacetic acid (0.377 mL). After stirring for 4 hours, the reaction was concentrated then dissolved in dichloromethane (3 mL) and treated with 1,3-difluoropropan-2-one (0.028 g) followed by sodium triacetoxyborohydride (0.078 g). After stirring for 4 hours, the reaction was quenched by the addition of saturated aqueous NaHCO<sub>3</sub> and dichloromethane (5 mL). The reaction was diluted with dichloromethane (250 mL) and saturated aqueous NaHCO<sub>3</sub> (100 mL) was added. The organic layer was separated, washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated. Trituration with acetonitrile gave the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.34 (s, 1H), 8.03 (s, 2H), 7.52 (d, 3H), 7.35 (d, 3H), 7.04 (d, 2H), 6.75-6.60 (m, 1H), 6.40 (s, 1H), 6.20 (s, 1H), 5.17-5.06 (m, 1H), 4.60 (d, 4H), 2.98 (d, 12H), 2.37-2.02 (m, 6H), 1.96 (s, 3H), 1.39 (s, 2H), 0.93 (s, 6H).

**Example 236**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 236A**

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(piperazin-1-ylamino)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 232D for EXAMPLE 1A in EXAMPLE 1B.

**Example 236B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(oxetan-3-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 236A for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (br. s, 1H), 9.20 (s, 1H), 8.53 (d, 1H), 8.04 (d, 1H),

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7.83 (dd, 1H), 7.53 (m, 4H), 7.34 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.39 (m, 1H), 6.18 (d, 1H), 4.55 (t, 2H), 4.44 (t, 2H), 3.47 (m, 1H), 3.06 (m, 4H), 2.88 (m, 4H), 2.74 (m, 4H), 2.09 (m, 11H), 1.38 (t, 2H), 0.91 (s, 6H).

**Example 237**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 236A for tert-butyl piperazine-1-carboxylate and dihydro-2H-pyran-4(3H)-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (br. s, 1H), 9.27 (d, 1H), 9.23 (s, 1H), 8.44 (m, 2H), 8.12 (d, 1H), 7.68 (m, 3H), 7.44 (m, 2H), 7.06 (m, 2H), 6.75 (dd, 1H), 6.51 (m, 2H), 4.02 (m, 2H), 3.31 (m, 2H), 3.06 (m, 4H), 2.91 (m, 5H), 2.76 (s, 2H), 2.38 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.65 (m, 2H), 1.39 (m, 7H), 0.93 (s, 6H).

**Example 238**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{(3R)-tetrahydrofuran-3-ylamino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 238A**

(R)-3-nitro-4-(tetrahydrofuran-3-ylamino)benzene-sulfonamide

The title compound was prepared by substituting (R)-tetrahydrofuran-3-amine for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

**Example 238B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{(3R)-tetrahydrofuran-3-ylamino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 238A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.47 (d, 1H), 8.19 (m, 2H), 7.97 (d, 1H), 7.74 (m, 1H), 7.52 (d, 1H), 7.46 (t, 1H), 7.34 (m, 2H), 7.05 (m, 2H), 6.96 (d, 1H), 6.89 (d, 1H), 6.65 (dd, 1H), 6.33 (m, 1H), 6.22 (d, 1H), 4.31 (m, 1H), 3.92 (m, 1H), 3.87 (m, 1H), 3.76 (m, 1H), 3.69 (m, 1H), 3.04 (m, 4H), 2.73 (m, 2H), 2.33 (m, 1H), 2.18 (m, 6H), 1.95 (m, 2H), 1.88 (m, 1H), 1.39 (t, 2H), 0.92 (s, 6H).

**Example 239**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 239A**

tert-butyl(4,4-difluorocyclohexyl)methylcarbamate

Tert-butyl(4-oxocyclohexyl)methylcarbamate (5 g) and diethylaminosulfur trifluoride (7.45 g) were stirred in dichloro-

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romethane (100 mL) for 24 hours. The mixture was quenched with pH 7 buffer (100 mL), and poured into ether (400 mL). The resulting solution was separated, and the organic layer was washed twice with water, and once with brine, and then concentrated to give the crude product and fluoroolefin by-product in a 3:2 ratio. The crude material was taken up in tetrahydrofuran (70 mL) and water (30 mL), and N-methylmorpholine-N-oxide (1.75 g), and OsO<sub>4</sub> (2.5 wt % solution in t-butanol) were added, and the mixture was stirred for 24 hours. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was then added, and the mixture was stirred for 30 minutes. The mixture was then diluted with ether (300 mL), and the resulting solution was separated, and rinsed twice with water, and once with brine, and concentrated. The crude product was chromatographed on silica gel using 5-10% ethyl acetate in hexanes to provide the title compound.

## Example 239B

(4,4-difluorocyclohexyl)methanamine

A solution of EXAMPLE 239A (3 g) in dichloromethane (35 mL), trifluoroacetic acid (15 mL), and triethylsilane (1 mL) was stirred for 2 hours. The solution was concentrated, then concentrated from toluene, and left on high vacuum for 24 hours. The semi-solid was taken up in ether/hexane and filtered to provide the title compound as its trifluoroacetic acid salt.

## Example 239C

4-((4,4-difluorocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 239B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 239D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenylsulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 239C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 12.40 (s, 1H), 11.61 (br s, 1H), 8.53 (m, 1H), 8.50 (d, 1H), 7.99 (d, 1H), 7.73 (d, 1H), 7.49 (m, 2H), 7.32 (d, 2H), 7.04 (d, 2H), 7.00 (d, 1H), 6.65 (d, 1H), 6.32 (s, 1H), 6.21 (s, 1H), 3.37 (m, 4H), 3.06 (m, 4H), 2.73 (m, 2H), 2.18 (m, 4H), 1.97 (m, 4H), 1.81 (m, 4H), 1.38 (m, 2H), 1.20 (m, 4H), 0.92 (s, 6H).

## Example 240

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 240A

4-(1-tert-butylpiperidin-4-ylamino)-3-(trifluoromethylsulfonyl)benzenesulfonamide

To a mixture of 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide (307 mg) and EXAMPLE 227A (156 mg)

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in tetrahydrofuran (4 mL) was added Hunig's Base (1 mL). The mixture was stirred for 3 days. The mixture was diluted with ethyl acetate (300 mL) and water (100 mL) and stirred until the solid disappeared into the solution. The layers were separated and the organic phase was washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the combined aqueous layers were extracted again with ethyl acetate and the combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was evaporated to provide the title compound.

## Example 240B

N-({4-[(1-tert-butylpiperidin-4-yl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 240A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.53 (s, 1H), 8.04 (s, 1H), 7.94 (d, 1H), 7.86 (m, 1H), 7.55 (d, 2H), 7.44 (d, 1H), 7.33 (m, 3H), 7.05 (d, 2H), 6.92 (m, 1H), 6.62 (dd, 1H), 6.43 (m, 1H), 6.29 (d, 2H), 3.79 (m, 1H), 3.05 (m, 6H), 2.73 (s, 3H), 2.19 (m, 8H), 1.96 (s, 3H), 1.27 (m, 12H), 0.92 (s, 6H).

## Example 241

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-(oxetan-3-yl)morpholin-2-yl)methyl]amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 241A

tert-butyl 2-((4-sulfamoyl-2-(trifluoromethylsulfonyl)phenylamino methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine and 4-fluoro-3-(trifluoromethylsulfonyl)benzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 1F.

## Example 241B

tert-butyl 2-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-(trifluoromethylsulfonyl)phenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 241A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G.

## Example 241C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-(morpholin-2-ylmethylamino)-3-(trifluoromethylsulfonyl)phenylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 241B for EXAMPLE 1A in EXAMPLE 1B.

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## Example 241D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({[4-(oxetan-3-yl)morpholin-2-yl]methyl}amino)-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 241C for tert-butyl piperazine-1-carboxylate and oxetan-3-one for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.15 (d, 1H), 8.04 (d, 1H), 7.92 (dd, 1H), 7.54 (d, 1H), 7.51 (t, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.25 (m, 1H), 7.04 (m, 3H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.19 (d, 1H), 4.54 (t, 2H), 4.43 (m, 2H), 3.85 (m, 1H), 3.69 (m, 1H), 3.52 (m, 1H), 3.48 (m, 1H), 3.39 (m, 2H), 3.07 (m, 4H), 2.77 (br s, 2H), 2.69 (d, 1H), 2.56 (d, 1H), 2.21 (br s, 4H), 2.15 (t, 2H), 1.94 (m, 3H), 1.76 (t, 1H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 242

N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 242A

5-chloro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 138D.

## Example 242B

N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methyl]amino)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 242A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 8.41 (d, 1H), 8.07 (d, 1H), 7.93 (d, 1H), 7.60 (d, 1H), 7.51-7.53 (m, 2H), 7.40 (s, 1H), 7.33-7.35 (m, 2H), 7.03-7.05 (m, 2H), 6.68 (dd, 1H), 6.42 (dd, 1H), 6.16 (d, 1H), 3.77 (d, 1H), 3.69-3.71 (m, 3H), 3.48-3.53 (m, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.14-2.20 (m, 6H), 1.96 (s, 2H), 1.65-1.76 (m, 4H), 1.38 (t, 2H), 0.93 (s, 6H).

## Example 243

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 243A

5-chloro-6-(1-cyclopropylpiperidin-4-ylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-chloro-3-nitrobenzenesulfonamide,

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1-cyclopropylpiperidin-4-amine for 4-methylpiperazin-1-amine dihydrochloride and Hunig's base for N<sup>1</sup>,N<sup>1</sup>,N<sup>2</sup>,N<sup>2</sup>-tetramethylethane-1,2-diamine in EXAMPLE 6A.

## Example 243B

N-({5-chloro-6-[(1-cyclopropylpiperidin-4-yl)amino]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 243A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.40 (d, 1H), 8.05 (d, 1H), 7.88 (d, 1H), 7.56 (d, 1H), 7.50 (m, 2H), 7.34 (d, 2H), 7.03 (d, 2H), 6.97 (br d, 1H), 6.66 (dd, 1H), 6.40 (m, 1H), 6.16 (d, 1H), 4.04 (m, 1H), 3.03 (br m, 6H), 2.73 (s, 2H), 2.42 (br m, 2H), 2.18 (br m, 6H), 1.95 (s, 2H), 1.80 (m, 3H), 1.62 (m, 2H), 1.38 (t, 2H), 0.91 (s, 6H), 0.47 (m, 2H), 0.40 (br m, 2H).

## Example 244

N-[(5-chloro-6-[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 244A

(S)-tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 244B

(S)-5-chloro-6-((morpholin-2-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244A for EXAMPLE 113A in EXAMPLE 134A.

## Example 244C

(S)-5-chloro-6-((4-(cyanomethyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

## Example 244D

N-[(5-chloro-6-[(2S)-4-(cyanomethyl)morpholin-2-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 244C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.99 (s, 1H), 9.09 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.55 (dd, 1H), 4.43 (dd, 1H), 4.05 (m, 1H), 3.85 (d, 1H), 3.76 (s, 2H), 3.63 (dt, 1H), 3.06 (m, 4H), 2.91 (d, 1H), 2.77 (s, 2H), 2.58 (d, 1H), 2.51-2.44 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 245**

N-[(5-chloro-6-[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-ylsulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 245A**

(S)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

**Example 245B**

N-[(5-chloro-6-[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-ylsulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 245A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.09 (d, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.11 (t, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (s, 1H), 6.54 (s, 1H), 6.49 (s, 1H), 4.85-4.46 (m, 3H), 4.45-3.87 (m, 3H), 3.50 (m, 1H), 3.37 (dd, 1H), 3.21 (m, 2H), 3.07 (m, 4H), 2.86 (t, 1H), 2.77 (s, 2H), 2.27 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 246**

N-[(5-chloro-6-[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy]pyridin-3-ylsulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 246A**

(R)-tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 2-(hydroxymethyl)-morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

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(R)-5-chloro-6-(morpholin-2-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 246A for EXAMPLE 113A in EXAMPLE 134A.

**Example 246C**

(R)-5-chloro-6-((4-(cyanomethyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 246B for EXAMPLE 134A and 2-bromoacetonitrile for methyl iodide in EXAMPLE 134B.

**Example 246D**

N-[(5-chloro-6-[(2R)-4-(cyanomethyl)morpholin-2-yl]methoxy]pyridin-3-ylsulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 246C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.99 (s, 1H), 9.09 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.55 (dd, 1H), 4.43 (dd, 1H), 4.05 (m, 1H), 3.85 (d, 1H), 3.76 (s, 2H), 3.63 (dt, 1H), 3.06 (m, 4H), 2.91 (d, 1H), 2.77 (s, 2H), 2.58 (d, 1H), 2.51-2.44 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

**Example 247**

N-[(5-chloro-6-[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-ylsulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 247A**

(R)-5-chloro-6-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 246B for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

**Example 247B**

N-[(5-chloro-6-[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methoxy]pyridin-3-ylsulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 247A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.09 (d, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.11 (t, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (s, 1H), 6.54 (s, 1H), 6.49 (s,



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1H), 4.85-4.46 (m, 3H), 4.45-3.87 (m, 3H), 3.50 (m, 1H), 3.37 (dd, 1H), 3.21 (m, 2H), 3.07 (m, 4H), 2.86 (t, 1H), 2.77 (s, 2H), 2.27 (m, 8H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 248

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 248A

5-bromo-3-fluoro-2-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine

The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl) methanol in EXAMPLE 24A.

## Example 248B

tert-butyl 5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

EXAMPLE 248A (0.308 g), tert-butyl carbamate (0.141 g), palladium(II) acetate (0.011 g), Xantphos (0.043 g) and cesium carbonate (0.489 g) were combined with dioxane (5.0 mL) in a 20-mL vial equipped with a magnetic stir bar. The vial was flushed with nitrogen, capped and stirred at 100° C. overnight. Additional palladium(II) acetate (0.011 g), Xantphos (0.043 g) and tert-butyl carbamate (0.141 g) were added and heating was continued at 100° C. for 8 hours. The cooled reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on silica gel with 7-25% ethyl acetate in hexanes as the eluent.

## Example 248C

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

Under ice-cooling, thionyl chloride (1.563 mL) was added dropwise over 20 minutes to water (9 mL). The mixture was stirred for 12 hours to give a SO<sub>2</sub>-containing solution. Separately, EXAMPLE 248B (0.295 g) was added to a mixture of 1,4-dioxane (3.2 mL) and concentrated HCl (8 mL) at 0° C. After stirring for 15 minutes, a solution of sodium nitrite (0.065 g) in water (2 mL) was added dropwise and stirring was continued at 0° C. for 3 hours. Copper(I) chloride (0.042 g) and then the freshly prepared solution of diazotized material were added sequentially to the previously prepared SO<sub>2</sub>-containing solution. The resulting solution was stirred for 30 minutes and then extracted with ethyl acetate (2×125 mL). The combined extracts were dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on silica gel with 5% ethyl acetate in hexanes as the eluent.

## Example 248D

5-fluoro-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 248C (0.08 g) in isopropanol (2 mL) at 0° C. was treated with ammonium hydroxide (1.697 mL), stirred

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overnight and then concentrated to dryness. The obtained solid was slurried in water, filtered, rinsed with water and dried under high vacuum to provide the title compound.

## Example 248E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-fluoro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 248D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.03 (d, 1H), 8.44 (dd, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.67 (m, 1H), 7.65 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.77 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.55 (d, 2H), 3.80 (m, 4H), 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.88 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 250

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 250A

5-chloro-6-((3-methyloxetan-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting (3-methyloxetan-3-yl)methanol for (tetrahydro-2H-pyran-4-yl) methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 250B

N-({5-chloro-6-[3-hydroxy-2-(hydroxymethyl)-2-methylpropoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 250A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.22 (d, 1H), 8.51 (d, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.66 (t, 2H), 7.43-7.46 (m, 2H), 7.04-7.09 (m, 2H), 6.75 (dd, 1H), 6.45-6.54 (m, 2H), 4.47 (s, 2H), 3.81-3.84 (m, 2H), 3.74 (d, 2H), 3.03-3.11 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10-2.17 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.16 (s, 3H), 0.94 (s, 6H).

## Example 251

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 251A

5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting (4-fluorotetrahydro-2H-pyran-4-yl)methanol for (tetrahydro-2H-

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pyran-4-yl)methanol and 5-bromo-6-chloropyridine-3-sulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 251B

6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

To a suspension of 5-bromo-6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide (200 mg) and cyclohexene (0.549 mL) in ethyl acetate (10 mL) was added 10% palladium on carbon (57.6 mg). The suspension was stirred for 60 minutes at 120° C. The reaction mixture was filtered and concentrated. The product was purified by reverse-phase flash chromatography (C18, 15 g, 10%-100% acetonitrile/H<sub>2</sub>O/trifluoroacetic acid 0.1%).

## Example 251C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([6-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 251B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 9.29 (d, 1H), 8.50 (dd, 1H), 8.41 (d, 1H), 8.07 (d, 1H), 7.66-7.70 (m, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.84 (d, 1H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.50 (d, 2H), 3.81-3.89 (m, 2H), 3.70-3.81 (m, 2H), 3.02-3.12 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.10-2.18 (m, 4H), 1.97 (s, 2H), 1.77-1.94 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 252

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 252A

tert-butyl 4-((1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and tert-butyl morpholin-2-ylmethylcarbamate for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 252B

(4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methanamine

A solution of EXAMPLE 252A (538 mg) in dioxane (4 mL) was treated with 4.0M HCl in dioxane solution (1.8 mL).

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The reaction was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and used without further purification.

## Example 252C

4-((4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 252B for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 252D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([4-(1,3-difluoropropan-2-yl)morpholin-2-yl]methyl)amino]-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 252C for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.59 (t, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.83 (dd, 1H), 7.51 (m, 3H), 7.33 (d, 2H), 7.07 (d, 1H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.39 (m, 1H), 6.19 (d, 1H), 4.69 (t, 2H), 4.57 (t, 2H), 3.85 (m, 1H), 3.70 (m, 1H), 3.52 (m, 2H), 3.41 (m, 2H), 3.07 (br s, 4H), 2.91 (d, 1H), 2.74 (m, 3H), 2.59 (m, 1H), 2.43 (m, 1H), 2.20 (m, 4H), 2.15 (m, 2H), 1.95 (br s, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

## Example 253

N-[(5-chloro-6-([1-(cyanomethyl)piperidin-4-yl]methoxy)pyridin-3-yl]sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 253A

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 253B

5-chloro-6-(piperidin-4-ylmethoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

The title compound was prepared by substituting EXAMPLE 253A for EXAMPLE 39A in EXAMPLE 39B.

## Example 253C

5-chloro-6-((1-(cyanomethyl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 253B (0.061 g), 2-chloroacetonitrile (0.017 g), sodium carbonate (0.025 g) and N,N-dimethylformamide (1 mL) were combined in a 4-mL vial and heated at 60° C. overnight. The cooled reaction mixture was diluted with ethyl

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acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on silica gel with 2-10% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 253D

N-[(5-chloro-6-[[1-(cyanomethyl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 253C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 9.14 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (t, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.74 (dd, 1H), 6.50 (m, 2H), 4.18 (d, 2H), 3.64 (s, 2H), 3.05 (s, 4H), 2.77 (m, 4H), 2.24 (m, 4H), 2.13 (m, 4H), 1.97 (s, 2H), 1.69 (m, 3H), 1.41 (m, 4H), 0.93 (s, 6H).

## Example 254

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 254A

(R)-tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)pyrrolidine-1-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 254B

(R)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 254A for EXAMPLE 113A in EXAMPLE 134A.

## Example 254C

(R)-4-(1-(2-(2-methoxyethoxy)ethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

To a solution of (R)-3-nitro-4-(pyrrolidin-3-ylamino)benzenesulfonamide (440 mg) in N,N-dimethylformamide (10 mL) was added sodium carbonate (132 mg) and 1-bromo-2-(2-methoxyethoxy)ethane (0.155 mL). The reaction mixture was heated at 60° C. for 18 hours and after an aqueous workup, the crude product was purified on silica gel with a 2.5-10% methanol in methylene chloride gradient to provide the title compound.

## Example 254D

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-(3R)-1-[2-(2-methoxyethoxy)ethyl]pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yl-oxy)benzamide

The title compound was prepared by substituting EXAMPLE 254C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.96 (m, 1H), 9.25 (m, 1H), 8.57 (d, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.82 (d, 1H), 6.76 (dd, 1H), 6.55 (m, 1H), 6.47 (m, 1H), 5.26 (br s, 1H), 4.02 (m, 1H), 3.63 (m, 4H), 3.53 (m, 2H), 3.28 (s, 3H), 3.07 (m, 4H), 2.89-2.81 (m, 2H), 2.78 (s, 2H), 2.75-2.66 (m, 3H), 2.37 (m, 1H), 2.26 (m, 2H), 2.24-2.18 (m, 1H), 2.15 (m, 4H), 1.97 (s, 2H), 1.65 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 255

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 255A

(R)-4-(1-(2-(dimethylamino)acetyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride, hydrochloric acid for 1-bromo-2-(2-methoxyethoxy)ethane in EXAMPLE 254C except the reaction was stirred at ambient temperature for 18 hours.

## Example 255B

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-(3R)-1-(N,N-dimethylglycyl)pyrrolidin-3-yl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 255A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.01 (d, 1H), 9.26 (m, 1H), 8.46-8.33 (m, 3H), 8.14 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.01-6.89 (m, 1H), 6.76 (dd, 1H), 6.55 (m, 1H), 6.48 (m, 1H), 5.32 (br s, 1H), 4.27-4.14 (m, 1H), 4.05-3.95 (m, 1H), 3.82-3.62 (m, 3H), 3.27-3.15 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.34 (2, 3H), 2.32 (s, 3H), 2.30-2.20 (m, 3H), 2.15 (m, 4H), 1.97 (s, 2H), 1.87-1.81 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 256

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-nitro-4-[[1-(oxetan-3-yl)azetidin-3-yl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 256A

tert-butyl 3-(2-nitro-4-sulfamoylphenylamino)azetidine-1-carboxylate

The title compound was prepared by substituting tert-butyl 3-aminoazetidine-1-carboxylate for 4-methylpiperazin-1-amine dihydrochloride in EXAMPLE 6A.

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Example 256B

4-(azetidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 256A for (S)-1-tert-butyl 2-methyl 4,4-difluoropyrrolidine-1,2-dicarboxylate in EXAMPLE 168A.

Example 256C

3-nitro-4-(1-(oxetan-3-yl)azetidin-3-ylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 256B for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

Example 256D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[1-(oxetan-3-yl)azetidin-3-yl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 256C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 9.27 (d, 1H), 8.62 (d, 1H), 8.42 (d, 1H), 8.35 (dd, 1H), 8.09 (d, 1H), 7.67 (m, 1H), 7.63 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.67 (d, 1H), 6.55 (d, 1H), 6.48 (dd, 1H), 4.66 (t, 2H), 4.58 (m, 2H), 4.23 (m, 1H), 3.71 (m, 3H), 3.12 (dd, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (t, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

Example 257

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 257A

tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 126A for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

Example 257B

5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

The title compound was prepared by substituting EXAMPLE 257A for EXAMPLE 39A in EXAMPLE 39B.

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Example 257C

5-chloro-6-((1-(cyanomethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

Example 257B (0.166 g) in acetonitrile (3 mL) was treated with 2-chloroacetonitrile (0.027 g) and sodium carbonate (0.064 g), heated at 60° C. overnight, cooled to room temperature and chromatographed on silica gel with 0 to 3% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent. The obtained solid was slurried in water, filtered, rinsed with water and diethyl ether, and dried in a vacuum oven at 80° C.

Example 257D

N-[(5-chloro-6-{[1-(cyanomethyl)-4-fluoropiperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 257C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.12 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 4.49 (d, 2H), 3.72 (s, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.73 (m, 4H), 2.26 (t, 2H), 2.13 (m, 4H), 2.07 (m, 2H), 1.90 (m, 4H), 1.39 (t, 2H), 0.93 (s, 6H).

Example 258

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Example 258A

(S)-tert-butyl

2-(tosyloxymethyl)morpholine-4-carboxylate

To a solution of (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (1 g) in dichloromethane (50 mL) was added triethylamine (1.604 mL) and 4-methylbenzene-1-sulfonyl chloride (1.097 g). The mixture was stirred at ambient temperature under nitrogen for 72 hours. The reaction was diluted with methylene chloride (50 mL) and brine (100 mL). The brine layer was extracted with methylene chloride (75 mL). The combined organics were dried over sodium sulfate, filtered and concentrated. The crude material was purified on a silica gel column eluting with a 15-65% ethyl acetate in hexane gradient to provide the title compound.

Example 258B

(S)-tert-butyl

2-(azidomethyl)morpholine-4-carboxylate

A solution of EXAMPLE 258A (1.66 g) and sodium azide (0.581 g) in anhydrous N,N-dimethylformamide (10 mL) was stirred at 90° C. for 4 hours. The mixture was cooled and concentrated to dryness. The residue was taken up in 5% aqueous sodium carbonate solution and extracted with meth-



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ylene chloride. The organic solution was dried (MgSO<sub>4</sub>), filtered and concentrated to give a solid.

## Example 258C

(R)-tert-butyl  
2-(aminomethyl)morpholine-4-carboxylate

This compound was obtained by hydrogenation of EXAMPLE 258B under 60 psi of hydrogen over 10% palladium on carbon in methanol for 24 hours, followed by filtration and evaporation of the solvent.

## Example 258D

(R)-tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 258C for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 258E

(S)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258D for EXAMPLE 113A in EXAMPLE 134A.

## Example 258F

(R)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258E for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

## Example 258G

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[4-([[(2R)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 258F for EXAMPLE 130C in EXAMPLE 130D.

<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

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## Example 259

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-{[4-([[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 259A

(R)-tert-butyl  
2-(tosyloxymethyl)morpholine-4-carboxylate

The title compound was prepared by substituting (R)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for (S)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate in EXAMPLE 258A.

## Example 259B

(R)-tert-butyl  
2-(azidomethyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 259A for EXAMPLE 258A in EXAMPLE 258B.

## Example 259C

(S)-tert-butyl  
2-(aminomethyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 259B for EXAMPLE 258B in EXAMPLE 258C.

## Example 259D

(S)-tert-butyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 259C for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 259E

(R)-4-(morpholin-2-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259D for EXAMPLE 113A in EXAMPLE 134A.

## Example 259F

(S)-4-((4-(2-(dimethylamino)acetyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259E for EXAMPLE 134A and 2-(dimethylamino)acetyl chloride hydrochloride for methyl iodide in EXAMPLE 134B.

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Example 259G

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S)-4-(N,N-dimethylglycyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 259F for EXAMPLE 130C in EXAMPLE 130D.

<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.27 (d, 1H), 8.87 (bs, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.10 (dd, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (dd, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 6.48 (s, 1H), 4.55 (dd, 1H), 4.20 (dd, 1H), 3.95-3.76 (m, 2H), 3.60-3.40 (m, 3H), 3.32 (dd, 1H), 3.25-3.12 (m, 2H), 3.07 (m, 4H), 2.80 (m, 1H), 2.77 (s, 2H), 2.26 (s, 6H), 2.23 (s, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 260

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 260A

5-chloro-6-((1-(2-(dimethylamino)acetyl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 253B (0.061 g), 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.061 g), and sodium carbonate (0.032 g) were combined in a 4-mL vial with N,N-dimethylformamide (2 mL). The mixture was stirred at ambient temperature for 3 days. Additional 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.037 g), sodium carbonate (0.032 g) and N,N-dimethylformamide (1 mL) were added and stirring was continued for 24 hours. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO<sub>4</sub>), filtered, concentrated and chromatographed on silica gel with 0 to 20% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 260B

N-[(5-chloro-6-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 260A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 12.91 (s, 1H), 9.16 (d, 1H), 8.75 (d, 1H), 8.51 (d, 1H), 8.33 (d, 1H), 7.70 (d, 1H), 7.62 (d, 1H), 7.45 (m, 2H), 7.09 (m, 2H), 6.77 (dd, 1H), 6.60 (d, 1H), 6.45 (d, 1H), 4.81 (d, 1H), 4.15 (m, 3H), 3.24 (m, 2H), 3.04 (m, 4H), 2.89 (m, 1H), 2.79 (s, 2H), 2.53 (m, 1H), 2.29 (m, 6H), 2.26 (m, 2H), 2.18 (m, 4H), 1.98 (m, 2H), 1.91 (m, 1H), 1.71 (m, 2H), 1.39 (t, 2H), 1.25 (m, 2H), 0.94 (s, 6H).

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Example 261

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 261A

(R)-tert-Butyl 3-(3-chloro-5-sulfamoylpyridin-2-yloxy)pyrrolidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 261B

(R)-5-Chloro-6-(pyrrolidin-3-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 261A for tert-butyl(4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

## Example 261C

(R)-5-chloro-6-(1-(2,2-difluoroethyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

A mixture of EXAMPLE 261B (353 mg), 1,1-difluoro-2-iodoethane (268 mg), sodium carbonate (283 mg) in N,N-dimethylformamide (10 mL) was heated at 80° C. overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with water, brine, dried over magnesium sulfate, filtered, and concentrated. The residue was loaded onto silica gel column and eluted using a gradient of 0.5 to 3% methanol in dichloromethane to provide the title compound.

## Example 261D

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]oxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 261C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.55 (s, 1H), 8.04 (s, 1H), 7.95 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.35 (m, 3H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.33 (m, 1H), 6.24 (d, 1H), 6.25-5.97 (m, 1H), 5.39 (m, 1H), 2.98 (m, 6H), 2.86 (m, 6H), 2.55 (m, 2H), 2.24 (m, 7H), 1.96 (s, 2H), 1.83 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 262

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 262A

(R)-4-(1-(cyanomethyl)pyrrolidin-3-ylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting 2-bromoacetonitrile for 1-bromo-2-(2-methoxyethoxy)ethane in EXAMPLE 254C.

## Example 262B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3R)-1-(cyanomethyl)pyrrolidin-3-yl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 262A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.27 (d, 1H), 8.53 (d, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.10 (d, 1H), 7.67-7.64 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.81 (d, 1H), 6.76 (dd, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 5.15 (br s, 1H), 4.10 (m, 1H), 3.89 (s, 2H), 3.07 (m, 4H), 2.93-2.86 (m, 2H), 2.80-2.77 (m, 3H), 2.61-2.53 (m, 1H), 2.31-2.21 (m, 3H), 2.14 (m, 4H), 1.97 (s, 2H), 1.75-1.68 (m, 1H), 1.39 (t, 2H), 0.94 (m, 6H).

## Example 263

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-[(5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 263A

tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate

Sodium hydride (6.63 g, 60% in mineral oil) was added to trimethylsulfoxonium iodide (36.5 g) in dimethyl sulfoxide (150 mL) and tetrahydrofuran (150 mL), was and stirred for 30 minutes. tert-Butyl 4-oxopiperidine-1-carboxylate (25.4 g) was added and the reaction was stirred for 3 hours. The reaction was poured into water (800 mL) and extracted three times with ether. The combined extracts were washed three times with water, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to yield the crude product which was used without further purification.

## Example 263B

tert-butyl 4-(2-(benzyloxy)benzyl)-4-hydroxypiperidine-1-carboxylate

(2-(Benzyloxy)phenyl)magnesium bromide (33.8 mL, 1M) was added to a solution of EXAMPLE 263A (6.0 g) and CuI (1.07 g) in tetrahydrofuran (220 mL) at 0° C. over 10 minutes. The reaction was quenched with pH 7 buffer (20

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mL), extracted twice with ether, and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 2-20% ethyl acetate in hexanes to provide the title compound.

## Example 263C

tert-butyl 4-hydroxy-4-(2-(hydroxybenzyl)piperidine-1-carboxylate

EXAMPLE 263B (11.5 g) and methanol (120 mL) were added to Raney Nickel (1.150 g) in a 250 mL SS pressure bottle and stirred for 1 hour at 30 psi under hydrogen. The mixture was filtered through a nylon membrane and the solution was concentrated to yield the title compound.

## Example 263D

tert-butyl 4-hydroxy-4-(2-(trifluoromethylsulfonyloxy)benzyl)piperidine-1-carboxylate

A mixture of EXAMPLE 263C (4.6 g), N-phenylbis(trifluoromethanesulfonimide) (5.88 g), and Hunig's base (2.88 mL) in dichloromethane (100 mL) was stirred for 24 hours. The mixture was concentrated and chromatographed on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

## Example 263E

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-hydroxypiperidine-1-carboxylate

A mixture of EXAMPLE 263D (4.3 g), 4-chlorophenylboronic acid (1.84 g), K<sub>3</sub>PO<sub>4</sub> (2.91 g), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.36 g) in 2-methyltetrahydrofuran (50 mL) was stirred at 70° C. for 24 hours. The reaction was cooled and quenched with water (50 mL), extracted twice with ether, and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-30% ethyl acetate in hexanes to provide the title compound.

## Example 263F

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidine-1-carboxylate

Sodium hydride (0.36 g, 60% in mineral oil) was added to EXAMPLE 263E (4.3 g), in tetrahydrofuran (40 mL) and the reaction was stirred for 10 minutes. Hexamethylphosphoramide (5 mL) and CH<sub>3</sub>I (2.34 mL) were added and the reaction was stirred at 50° C. for 18 hours. The reaction was cooled and quenched with water (50 mL), extracted twice with ether, and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-25% ethyl acetate in hexanes to provide the title compound.

## Example 263G

4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidine

The title compound was prepared by substituting EXAMPLE 263F for EXAMPLE 1A in EXAMPLE 1B.

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## Example 263H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-  
((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoate

A solution of EXAMPLE 263G (1.4 g), EXAMPLE 3H (1.06 g) and Hunig's base (0.75 mL) in dimethylsulfoxide (20 mL) was stirred at 120° C. for 18 hours. The reaction was cooled and quenched with water (200 mL), extracted three times with ether, and the combined extracts were washed three times with water, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

## Example 263I

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 263H for EXAMPLE 31 in EXAMPLE 3J.

## Example 263J

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 263I for EXAMPLE 1E and EXAMPLE 96A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.58 (br s, 1H), 8.58 (d, 1H), 8.28 (d, 1H), 8.05 (d, 1H), 7.56 (d, 1H), 7.52 (m, 1H), 7.46 (d, 1H), 7.44 (d, 2H), 7.28 (m, 5H), 7.11 (dd, 1H), 6.62 (dd, 1H), 6.41 (dd, 1H), 6.11 (d, 1H), 4.54 (d, 2H), 3.75 (m, 2H), 3.59 (m, 2H), 3.20 (m, 2H), 2.97 (s, 3H), 2.81 (m, 2H), 2.74 (m, 2H), 1.89 (m, 2H), 1.83 (m, 2H), 1.36 (m, 2H), 1.09 (m, 2H).

## Example 264

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-methoxypiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 263I for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.40 (br s, 1H), 8.62 (t, 1H), 8.58 (d, 1H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.54 (m, 2H), 7.44 (m, 3H), 7.28 (m, 5H), 7.13 (dd, 1H), 6.62 (dd, 1H), 6.41 (dd, 1H), 6.11 (d, 1H), 3.85 (dd, 2H), 3.31 (m, 4H), 3.20 (m, 2H), 2.97 (s, 3H), 2.81 (m, 2H), 2.73 (m, 2H), 1.89 (m, 1H), 1.62 (m, 2H), 1.38 (m, 2H), 1.25 (m, 2H), 1.09 (m, 2H).

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## Example 265

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 265A

benzyl 4-(piperidin-1-ylmethylene)piperidine-1-carboxylate

To a solution of benzyl 4-formylpiperidine-1-carboxylate (12.5 g) in toluene (120 mL) was added piperidine (6.46 g). The mixture was stirred at reflux under a Dean-Stark trap overnight. The mixture was then concentrated under vacuum and the residue was used directly in the next step.

## Example 265B

benzyl  
9-oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylate

To a solution of EXAMPLE 265A (15.88 g) in ethanol (300 mL) was added but-3-enone (3.89 g). The mixture was stirred at reflux overnight. Then acetic acid (30 mL) was added to the mixture which was stirred at reflux again overnight. The mixture was then concentrated under vacuum and the residue was diluted with ethyl acetate (400 mL) and washed with water and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, column purification gave the title compound.

## Example 265C

benzyl  
9-hydroxy-3-azaspiro[5.5]undecane-3-carboxylate

EXAMPLE 265B (21 g) and tetrahydrofuran (160 mL) were added to 5% Pt—C wet (3.15 g) in a 250 mL pressure bottle and stirred for 1 hour at 30 psi and room temperature. The mixture was filtered through a nylon membrane and the filtrate was concentrated under vacuum to provide the title compound.

## Example 265D

benzyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate

To a solution of EXAMPLE 265C (8.0 g) in dichloromethane (200 mL) was added Dess-Martin Periodinane (11.2 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with 2N aqueous NaOH, water, and brine. After drying over Na<sub>2</sub>SO<sub>4</sub> and filtration, concentration of the solvent gave the crude product which was used directly in the next reaction without further purification.

## Example 265E

benzyl 9-chloro-8-formyl-3-azaspiro[5.5]undec-8-ene-3-carboxylate

Phosphorus oxychloride (2.33 mL) was added dropwise to a cooled (0° C.) solution of EXAMPLE 265D (7.5 g) in N,N-dimethylformamide (10 mL) and dichloromethane (30



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mL). The mixture was then stirred overnight before it was diluted with ethyl acetate (300 mL) and washed with aqueous sodium acetate, water (3×), and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the crude product was used directly in the next reaction without further purification.

## Example 265F

benzyl 9-(4-chlorophenyl)-8-formyl-3-azaspiro[5.5]  
undec-8-ene-3-carboxylate

To a mixture of 4-chlorophenylboronic acid (5.94 g), EXAMPLE 265E (11.01 g), palladium(II) acetate (142 mg), K<sub>2</sub>CO<sub>3</sub> (13.2 g) and tetrabutylammonium bromide (10.2 g) was added water (120 mL). The mixture was stirred at 50° C. overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with water (3×) and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the residue was loaded on a column and eluted with 5 to 20% ethyl acetate in hexane to provide the title compound.

## Example 265G

benzyl 8-((4-(3-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(methoxycarbonyl)phenyl)piperazin-1-yl)methyl)-9-(4-chlorophenyl)-3-azaspiro[5.5]undec-8-ene-3-carboxylate

To a solution of EXAMPLE 15F (1.37 g) and EXAMPLE 265F (1.65 g) in dichloromethane (20 mL) was added sodium triacetoxyborohydride (1.24 g). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous NaOH, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

## Example 265H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

EXAMPLE 265G (2 g) and tetrahydrofuran (10 mL) were added to 20% Pd(OH)<sub>2</sub>—C, wet (0.400 g) in a 50 mL pressure bottle and stirred for 16 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and evaporation of the solvent gave the title compound.

## Example 265I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 265H (320 mg) in dichloromethane (5 mL) was added 1, 3-difluoroacetone (139 mg) and sodium triacetoxyborohydride (157 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous NaOH, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

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## Example 265J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

To a solution of EXAMPLE 265I (320 mg) in tetrahydrofuran (4 mL) and methanol (2 mL) was added LiOH·H<sub>2</sub>O (120 mg) and the solution was stirred overnight. The reaction was cooled, carefully neutralized with 1N aqueous HCl and extracted with dichloromethane (3×50 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered and concentrated under vacuum to provide the title compound.

## Example 265K

4-(4-{{9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 265J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.61 (s, 1H), 8.49 (d, 2H), 7.72 (m, 1H), 7.49 (m, 2H), 7.32 (d, 2H), 7.07 (m, 3H), 6.65 (dd, 1H), 6.35 (d, 1H), 6.20 (m, 1H), 4.66 (m, 2H), 4.50 (m, 2H), 3.84 (m, 2H), 3.04 (m, 5H), 2.70 (m, 6H), 2.23 (m, 6H), 2.00 (m, 4H), 1.35 (m, 12H).

## Example 266

4-(4-{{9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl}methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 266A

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

To a solution of EXAMPLE 265H (320 mg) in dichloromethane (5 mL) was added acetone (143 mg) and sodium triacetoxyborohydride (157 mg). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (200 mL) and washed with 2N aqueous NaOH, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

## Example 266B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 266A for EXAMPLE 265I in EXAMPLE 265J.

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## Example 266C

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.54 (s, 1H), 8.38 (m, 2H), 7.93 (d, 1H), 7.60 (m, 3H), 7.39 (m, 4H), 7.09 (d, 2H), 6.85 (d, 1H), 6.63 (dd, 1H), 6.27 (dd, 2H), 3.84 (m, 3H), 3.08 (m, 8H), 2.71 (s, 3H), 2.15 (m, 8H), 1.71 (m, 9H), 1.24 (m, 11H)

## Example 267

4-(4-{[9-(4-chlorophenyl)-3-(1,3-difluoropropan-2-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 265J for EXAMPLE 1E and EXAMPLE 40B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.56 (s, 1H), 8.38 (s, 1H), 8.06 (m, 1H), 7.57 (d, 1H), 7.38 (m, 5H), 7.07 (m, 3H), 6.64 (dd, 1H), 6.33 (d, 1H), 6.23 (m, 1H), 4.68 (d, 2H), 4.52 (d, 2H), 4.21 (d, 2H), 3.86 (dd, 2H), 3.08 (m, 8H), 2.71 (m, 6H), 2.10 (m, 12H), 1.42 (m, 7H).

## Example 268

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E and EXAMPLE 40B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.49 (s, 1H), 8.28 (d, 1H), 7.94 (dd, 2H), 7.60 (d, 1H), 7.35 (m, 4H), 7.08 (m, 2H), 6.61 (dd, 1H), 6.28 (dd, 2H), 4.18 (d, 2H), 3.85 (m, 2H), 3.05 (m, 7H), 2.71 (s, 3H), 2.25 (m, 6H), 2.02 (m, 2H), 1.63 (m, 8H), 1.30 (m, 9H).

## Example 269

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 269A

5-chloro-6-((4-fluoro-1-methylpiperidin-4-yl)methoxy)pyridine-3-sulfonamide

Example 257B (0.131 g) in N,N-dimethylformamide (3.0 mL) was treated with iodomethane (0.043 g) and sodium carbonate (0.079 g) and stirred at ambient temperature for 3 days. The N,N-dimethylformamide was removed on high

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vacuum and the concentrate was chromatographed on amine functionalized silica gel with 0 to 2% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 269B

N-({5-chloro-6-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 269A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.11 (d, 1H), 8.71 (d, 1H), 8.44 (d, 1H), 8.16 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.49 (dd, 1H), 4.49 (d, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.68 (m, 2H), 2.38 (m, 2H), 2.26 (m, 5H), 2.14 (t, 4H), 1.97 (m, 6H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 270

N-[(5-chloro-6-({[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy})pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 270A

5-chloro-6-((1-(2-(dimethylamino)acetyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

Example 257B (0.131 g), 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.139 g), and sodium carbonate (0.048 g) were combined in a 5-mL vial with N,N-dimethylformamide (3.0 mL) and stirred overnight at ambient temperature. Additional sodium carbonate (0.048 g) was added followed by 2-(dimethylamino)acetyl chloride, hydrochloric acid (0.139 g) and stirring was continued over a second night. The reaction mixture was concentrated under high vacuum, slurried in CH<sub>2</sub>Cl<sub>2</sub>, filtered, concentrated and chromatographed on amine functionalized silica gel with 0 to 4% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 270B

N-[(5-chloro-6-({[1-(N,N-dimethylglycyl)-4-fluoropiperidin-4-yl]methoxy})pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 270A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 9.12 (d, 1H), 8.73 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.52 (d, 1H), 6.49 (dd, 1H), 4.66 (d, 1H), 4.52 (dd, 2H), 4.07 (d, 1H), 3.46 (m, 1H), 3.40 (m, 1H), 3.30 (m, 1H), 3.11 (m, 1H), 3.06 (m, 4H), 2.77 (s, 2H), 2.35 (s, 6H), 2.26 (t, 2H), 2.14 (m, 4H), 2.05 (m, 2H), 1.97 (s, 2H), 1.81 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 271

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 271A

tert-butyl 4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidine-1-carboxylate

A solution of EXAMPLE 263E (2.0 g) and diethylamino-sulfur trifluoride (1.39 mL) in dichloromethane (40 mL) was stirred for 24 hours. The reaction was quenched with water (30 mL), extracted twice with ether, and the combined extracts were washed with water, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 5% ethyl acetate in hexanes to provide the title compound.

## Example 271B

4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidine

The title compound was prepared by substituting EXAMPLE 271A for EXAMPLE 1A in EXAMPLE 1B.

## Example 271C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 271B for EXAMPLE 263G in EXAMPLE 263H.

## Example 271D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((4'-chlorobiphenyl-2-yl)methyl)-4-fluoropiperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 271C for EXAMPLE 3I in EXAMPLE 3J.

## Example 271E

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 271D for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 11.46 (br s, 1H), 8.62 (t, 1H), 8.56 (d, 1H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.52 (m, 3H), 7.44 (d, 2H), 7.28 (m, 5H), 7.14 (m, 1H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.19 (d, 1H), 3.84 (dd, 2H),

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3.31 (m, 9H), 2.95 (d, 2H), 2.81 (m, 2H), 1.91 (m, 1H), 1.62 (m, 2H), 1.45 (m, 2H), 1.29 (m, 2H).

## Example 272

4-{4-[(4'-chlorobiphenyl-2-yl)methyl]-4-fluoropiperidin-1-yl}-N-({5-chloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]pyridin-3-yl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 271D for EXAMPLE 1E and EXAMPLE 96A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.64 (br s, 1H), 8.58 (m, 1H), 8.25 (m, 1H), 8.03 (d, 1H), 7.70 (dd, 1H), 7.50 (m, 4H), 7.43 (m, 3H), 7.28 (m, 4H), 7.15 (m, 1H), 6.68 (dd, 1H), 6.40 (dd, 1H), 6.19 (d, 1H), 4.54 (d, 2H), 4.04 (m, 1H), 3.75 (m, 2H), 3.58 (m, 2H), 2.95 (d, 2H), 2.80 (m, 2H), 1.88 (m, 2H), 1.82 (m, 2H), 1.48 (m, 2H), 1.28 (m, 2H), 0.85 (m, 2H).

## Example 273

4-(4-{[9-(4-chlorophenyl)-3-isopropyl-3-azaspiro[5.5]undec-8-en-8-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-(trifluoromethyl)phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 266B for EXAMPLE 1E and EXAMPLE 42A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.57 (s, 1H), 7.97 (d, 1H), 7.77 (s, 1H), 7.55 (m, 2H), 7.45 (m, 1H), 7.36 (m, 3H), 7.08 (d, 2H), 6.62 (dd, 2H), 6.35 (dd, 1H), 6.21 (d, 1H), 3.82 (m, 3H), 3.06 (m, 9H), 2.72 (m, 3H), 2.25 (m, 8H), 2.09 (m, 2H), 1.56 (m, 9H), 1.20 (m, 10H).

## Example 274

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 274A

(R)-5-chloro-6-(1-(3-fluoro-2-(fluoromethyl)propyl)pyrrolidin-3-yloxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 261B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 274B

N-[(5-chloro-6-[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]oxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 274A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.52 (s, 1H), 8.32 (d, 1H), 8.01 (d, 1H), 7.93 (d, 1H), 7.59 (d, 1H), 7.42 (m,

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1H), 7.33 (m, 3H), 7.05 (d, 2H), 6.63 (dd, 1H), 6.31 (dd, 1H), 6.25 (d, 1H), 5.38 (m, 1H), 4.65 (t, 2H), 4.53 (t, 2H), 3.02 (s, 4H), 2.94 (m, 5H), 2.75 (s, 2H), 2.66 (m, 1H), 2.23 (m, 7H), 1.96 (s, 2H), 1.82 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 275

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 275A

## 3-(2-(benzyloxy)ethoxy)tetrahydrofuran

Tetrahydrofuran-3-ol (0.881 g) in tetrahydrofuran (15 mL) was treated with 60% sodium hydride (0.8 g). After 10 minutes, ((2-bromoethoxy)methyl)benzene (3.23 g) was added. The solution was stirred for 16 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was separated, and was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 1:1 ethyl acetate:hexane to provide the title compound.

## Example 275B

## 2-(tetrahydrofuran-3-yloxy)ethanol

Example 275A (0.85 g) and 5% palladium on carbon (0.1 g) in ethanol (10 mL) was treated with a balloon of hydrogen. The reaction was stirred overnight. The solid was filtered off, and the filtrate was concentrated to give the title compound.

## Example 275C

## 3-nitro-4-(2-(tetrahydrofuran-3-yloxy)ethoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 275B for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 275D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({3-nitro-4-[2-(tetrahydrofuran-3-yloxy)ethoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 275C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.32 (s, 1H), 8.00-8.02 (m, 2H), 7.49-7.52 (m, 2H), 7.39-7.41 (m, 1H), 7.38 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.33-4.35 (m, 2H), 4.18-4.21 (m, 1H), 3.62-3.67 (m, 4H), 3.09 (s, 4H), 2.83 (s, 2H), 2.26 (s, 2H), 2.15 (s, 2H), 1.96 (s, 2H), 1.85-1.94 (m, 2H), 1.39 (t, 2H), 0.92 (s, 6H).

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## Example 276

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((trans-4-cyanocyclohexyl)methyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 276A

## trans-4-(aminomethyl)cyclohexanecarbonitrile

To a solution of tert-butyl(trans-4-(cyanomethyl)cyclohexyl)methylcarbamate (500 mg) in dichloromethane (10 mL) was slowly added trifluoroacetic acid (2 mL) at 0° C. The reaction mixture was warmed to room temperature, stirred for 1 hour and concentrated to provide the title compound.

## Example 276B

## 4-((trans-4-cyanocyclohexyl)methylamino)-3-nitrobenzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (347 mg) and EXAMPLE 276A (300 mg) in tetrahydrofuran (20 mL) was treated with triethylamine (1.4 mL) overnight and concentrated. The residue was triturated with ethyl acetate to provide the title compound.

## Example 276C

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((trans-4-cyanocyclohexyl)methyl)amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 276B in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.36 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.47-7.54 (m, 3H), 7.34 (d, 2H), 7.01-7.09 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.25 (t, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.57-2.68 (m, 1H), 2.17 (d, 6H), 1.92-2.06 (m, 4H), 1.78 (d, 2H), 1.66 (s, 1H), 1.35-1.53 (m, 4H), 0.96-1.10 (m, 2H), 0.92 (s, 6H).

## Example 277

N-[(5-chloro-6-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 277A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred



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for 24 hours. The organic layer was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated to give the product.

## Example 277B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 277A (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

## Example 277C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl) methanol

To a mixture of  $\text{LiBH}_4$  (13 g), EXAMPLE 277B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

## Example 277D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 277C (29.3 g) and triethylamine (30 mL) in  $\text{CH}_2\text{Cl}_2$  (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 277E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 277D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous  $\text{Na}_2\text{CO}_3$  solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give the product.

## Example 277F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours.

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The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 277G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 277F (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M NaOH (69 mL) was added, followed by 30%  $\text{H}_2\text{O}_2$  (8.43 mL), and the solution was stirred for 1 hour.  $\text{Na}_2\text{S}_2\text{O}_3$  (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid  $\text{NaH}_2\text{PO}_4$ . The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 277H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 277G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and  $\text{K}_3\text{PO}_4$  (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 277I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 277H (1.55 g), EXAMPLE 277E (2.42 g), and  $\text{HK}_2\text{PO}_4$  (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed three times with 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 277J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

Example 277I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to  $\text{NaH}_2\text{PO}_4$  solution, and extracted three times

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with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 277K

## 5,6-dichloropyridine-3-sulfonamide

To a solution of 5,6-dichloropyridine-3-sulfonyl chloride (32.16 g) in isopropyl alcohol (300 mL) at 0° C. was added a 30% aqueous solution of NH<sub>4</sub>OH (50.8 mL). After stirring overnight, the solvent was reduced to 1/3 of the original volume. It was then partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was chromatographed on silica gel. The material was then slurried in 1:9 ethyl acetate/hexanes, filtered and dried under vacuum to give the title compound.

## Example 277L

## tert-butyl

## 4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.0 g) in tetrahydrofuran (5 mL) was treated with 1.0 N LiAlH<sub>4</sub> in tetrahydrofuran (2.54 mL) at 0° C. The reaction mixture was stirred at room temperature for 2 hours. Water (0.6 mL) was added to the reaction mixture drop-wise, followed by 2 N aqueous NaOH (0.2 mL). The reaction was stirred for another 1 hour. The solid was removed by filtration via a pack of diatomaceous earth and washed with ethyl acetate. The filtrate was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 277M

## tert-butyl 4-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-4-fluoropiperidine-1-carboxylate

To a solution of EXAMPLE 277L (1 g) in tetrahydrofuran (15 mL) was added NaH (60% dispersion in mineral oil, 685 mg), and the solution was stirred for 10 minutes. EXAMPLE 227K (1 g) was added and the reaction stirred for 24 hours. The mixture was poured into water, neutralized with 10% HCl, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel eluting with 30% ethyl acetate in hexanes.

## Example 277N

## 5-chloro-6-((4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide ditrifluoroacetic acid

EXAMPLE 277M (13 mL) was treated with trifluoroacetic acid (2.363 mL), stirred at ambient temperature for 2 hours, concentrated and dried to give the title compound.

## Example 277O

## 5-chloro-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 277N (0.088 g) and oxetan-3-one (0.014 g) were combined in dichloromethane (2.0 mL) and dimethyl-

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formamide (1.0 mL) and stirred at ambient temperature for 45 minutes. Sodium triacetoxyborohydride (0.064 g) was added in portions. Stirring was continued overnight at ambient temperature. Additional oxetan-3-one (0.014 g) was added and stirring was continued for 30 minutes at ambient temperature before more sodium triacetoxyborohydride (0.064 g) was added. The reaction mixture was stirred for 72 hours at ambient temperature, concentrated, chromatographed on silica gel with 0 to 5% methanol in dichloromethane as the eluent, and dried in a vacuum oven at 80° C. to give the title compound.

## Example 277P

## N-[(5-chloro-6-[[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

EXAMPLE 277J (0.063 g), EXAMPLE 277O (0.042 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.032 g), and 4-dimethylaminopyridine (0.027 g) were combined in a 4-mL vial with dichloromethane (1.0 mL) and stirred overnight at ambient temperature. The reaction mixture was chromatographed directly without aqueous workup on silica gel with 0-4% methanol in dichloromethane as the eluent. Fractions containing the desired product were concentrated, slurried in acetonitrile, concentrated and dried overnight in a vacuum oven at 80° C. to give the title compound. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.13 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.67 (m, 1H), 7.66 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.51 (m, 2H), 4.63 (m, 4H), 4.53 (d, 2H), 3.39 (m, 1H), 3.07 (m, 4H), 2.77 (s, 2H), 2.51 (m, 2H), 2.25 (m, 2H), 2.18 (m, 2H), 2.13 (m, 4H), 2.06 (t, 2H), 1.97 (s, 2H), 1.89 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 278

## 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 278A

## 5-bromo-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-(tetrahydro-2H-pyran-4-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 36B.

## Example 278B

## 5-cyano-6-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 278A for EXAMPLE 36B in EXAMPLE 36C.

## Example 278C

## 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-({5-cyano-6-[2-(tetrahydro-2H-pyran-4-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 278B for EXAMPLE 11B in EXAMPLE 11D.

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<sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 7.96 (d, 1H), 7.56 (d, 1H), 7.45-7.47 (m, 1H), 7.40 (s, 1H), 7.36 (d, 2H), 7.06 (d, 2H), 6.67 (dd, 1H), 6.34 (dd, 1H), 6.25 (d, 1H), 4.47 (d, 2H), 3.80-3.84 (m, 2H), 3.24-3.28 (m, 2H), 3.12 (s, 2H), 2.16 (s, 2H), 1.97 (s, 2H), 1.61-1.71 (m, 4H), 1.40 (t, 2H), 1.21-1.25 (m, 2H), 0.93 (s, 6H).

## Example 279

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 279A

4-(furan-3-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting furan-3-ylmethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 279B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(3-furylmethoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 279A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.34 (s, 1H), 8.03-8.06 (m, 2H), 7.83 (s, 1H), 7.69 (t, 1H), 7.51-7.53 (m, 4H), 7.34-7.36 (m, 2H), 7.04-7.06 (m, 2H), 6.68 (dd, 1H), 6.57 (s, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 5.23 (s, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.15-2.32 (m, 6H), 1.39 (t, 2H), 0.92 (s, 6H).

## Example 280

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 280A

(R)-tert-butyl 3-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)pyrrolidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and (R)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 280B

(R)-5-chloro-6-(pyrrolidin-3-ylmethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 280A for tert-butyl(4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

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## Example 280C

(R)-5-chloro-6-((1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 280B for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 280D

N-[(5-chloro-6-{[(3R)-1-(1,3-difluoropropan-2-yl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 280C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.57 (s, 1H), 8.38 (d, 1H), 8.07 (d, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.44 (m, 1H), 7.35 (m, 3H), 7.05 (d, 2H), 6.64 (dd, 1H), 6.33 (dd, 1H), 6.23 (d, 1H), 4.65 (d, 2H), 4.53 (dd, 2H), 2.92 (m, 8H), 2.75 (m, 4H), 2.58 (m, 2H), 2.20 (m, 6H), 1.96 (m, 4H), 1.53 (m, 1H), 1.39 (t, 2H), 0.89 (s, 6H).

## Example 281

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 281A

(R)-5-chloro-6-((1-(2,2-difluoroethyl)pyrrolidin-3-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 280B for EXAMPLE 261B in EXAMPLE 261C.

## Example 281B

N-[(5-chloro-6-{[(3R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 281A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.59 (s, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.98 (d, 1H), 7.56 (d, 1H), 7.46 (m, 1H), 7.41 (d, 1H), 7.34 (d, 2H), 7.04 (d, 2H), 6.65 (dd, 1H), 6.35 (dd, 1H), 6.23 (m, 1H), 6.03 (m, 1H), 3.06 (s, 4H), 2.84 (m, 6H), 2.63 (m, 4H), 2.20 (m, 6H), 1.94 (m, 3H), 1.53 (m, 1H), 1.39 (t, 2H), 0.91 (s, 6H).

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## Example 282

N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 282A

5-chloro-6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.088 g) and 1,3-difluoropropan-2-one (0.028 g) were combined in dichloromethane (2 mL) and N,N-dimethylformamide (0.500 mL) and stirred at ambient temperature for 45 minutes. Sodium triacetoxyborohydride (0.064 g) was added in portions and then the reaction mixture was stirred overnight at ambient temperature. Additional 1,3-difluoropropan-2-one (0.028 g) was added, followed 30 minutes later by the addition of more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred at ambient temperature for 72 hours. Additional 1,3-difluoropropan-2-one (0.028 g) was again added, followed 30 minutes later by the addition of more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred overnight at ambient temperature. Additional 1,3-difluoropropan-2-one (0.028 g) was again added, followed 30 minutes later by the addition of more sodium triacetoxyborohydride (0.064 g). The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated under high vacuum to remove N,N-dimethylformamide and then chromatographed on silica gel with 0 to 4% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 282B

N-[(5-chloro-6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 282A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.12 (t, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 4.77 (dd, 1H), 4.65 (dd, 1H), 4.52 (dd, 2H), 3.06 (m, 4H), 2.93 (t, 1H), 2.80 (m, 5H), 2.52 (m, 1H), 2.26 (t, 2H), 2.13 (m, 4H), 2.04 (m, 2H), 1.97 (s, 2H), 1.85 (m, 2H), 1.39 (t, 2H), 1.28 (m, 2H), 0.93 (s, 6H).

## Example 283

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 283A

3-chloro-4-((4-fluoro-1-methylpiperidin-4-yl)methoxy)benzenesulfonamide

To a solution of (4-fluoro-1-methylpiperidin-4-yl)methanol (0.265 g) in tetrahydrofuran (2 mL) was added sodium

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hydride (0.288 g). After 15 minutes, 3-chloro-4-fluorobenzenesulfonamide (0.377 g) was added as a solution in tetrahydrofuran (1 mL). The reaction was stirred for 2 hours, quenched with water (5 mL), adjusted to pH~7 with 1N aqueous HCl, and extracted with dichloromethane (2×25 mL). The organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.1% to 10% methanol containing 2N NH<sub>3</sub>/dichloromethane over 30 minutes gave the title compound.

## Example 283B

N-({3-chloro-4-[(4-fluoro-1-methylpiperidin-4-yl)methoxy]phenyl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 283A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 10.68-9.84 (m, 1H), 7.99 (d, 1H), 7.79 (d, 1H), 7.63 (t, 1H), 7.54 (d, 1H), 7.50-7.38 (m, 2H), 7.34 (d, 2H), 7.04 (d, 3H), 6.64 (dd, 1H), 6.36 (dd, 1H), 6.22 (s, 1H), 4.23 (d, 2H), 3.03 (s, 6H), 2.71 (m, 4H), 2.07 (m, 12H), 1.38 (s, 3H), 1.24 (s, 2H), 0.92 (s, 6H).

## Example 284

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 284A

3-cyano-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

To a solution of (tetrahydro-2H-pyran-4-yl)methanol (0.258 g) in tetrahydrofuran (5 mL) was added sodium hydride (0.355 g) and the reaction stirred at room temperature for 15 minutes. EXAMPLE 52A (0.400 g) was added and the reaction stirred for an additional 1 hour. The reaction was poured into ethyl acetate (50 mL) and 1N aqueous HCl (35 mL). The organic layer was washed with brine (35 mL) dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 10% to 100% ethyl acetate/hexanes over 30 minutes gave the title compound.

## Example 284B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 284A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.60-11.16 (m, 1H), 8.15 (s, 1H), 8.08-8.01 (m, 2H), 7.58-7.46 (m, 3H), 7.35 (d, J=8.4, 2H), 7.29 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.40 (dd, 1H),



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6.20 (s, 1H), 4.05 (d, 2H), 3.89 (d, 2H), 3.37 (d, 4H), 3.09 (s, 4H), 2.81 (s, 2H), 2.21 (d, 7H), 1.96 (s, 2H), 1.67 (d, 2H), 1.39 (s, 2H), 0.92 (s, 6H).

## Example 285

N-[(5-chloro-6-[[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 285A

5-chloro-6-((1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 257B (0.263 g), 1,1-difluoro-2-iodoethane (0.23 g), and sodium carbonate (0.254 g) were combined in a 20-mL vial with N,N-dimethylformamide (6 mL) and stirred at 70° C. overnight. The reaction mixture was concentrated under high vacuum and then chromatographed on silica gel with 0 to 5% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent.

## Example 285B

N-[(5-chloro-6-[[1-(2,2-difluoroethyl)-4-fluoropiperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 285A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 9.12 (d, 1H), 8.72 (d, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.66 (m, 2H), 7.43 (m, 2H), 7.06 (m, 2H), 6.75 (dd, 1H), 6.50 (m, 2H), 6.18 (tt, 2H), 4.51 (d, 2H), 3.07 (m, 4H), 2.80 (m, 6H), 2.60 (td, 2H), 2.25 (t, 2H), 2.13 (m, 4H), 2.03 (t, 2H), 1.97 (s, 2H), 1.93 (m, 1H), 1.85 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 286

N-([3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 286A

3-chloro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (4-fluoro-1-methylpiperidin-4-yl) methanol in EXAMPLE 283A.

## Example 286B

N-([3-chloro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl)sulfonyl)-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 286A for

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EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.56-11.16 (m, 1H), 8.06 (d, 1H), 7.90 (d, 1H), 7.81 (d, 1H), 7.64-7.45 (m, 3H), 7.34 (d, 2H), 7.26 (d, 1H), 7.04 (d, 2H), 6.68 (d, 1H), 6.42 (dd, 1H), 6.18 (s, 1H), 4.28 (d, 2H), 3.78 (d, 2H), 3.61 (dd, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.17 (d, 6H), 1.87 (dd, 6H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 287

N-([5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 287A

(4,4-difluorocyclohexyl)methanol

Ethyl 4,4-difluorocyclohexanecarboxylate (1.0 g, 5.20 mmol) in diethyl ether (2 mL) was added dropwise to lithium aluminium hydride (0.24 g) in diethyl ether (15 mL), and heated under reflux for 4 hours. The reaction was then cooled to 0° C., and water was added (0.24 mL), followed by 5N aqueous NaOH (0.24 mL) and water (0.72 mL). Then Na<sub>2</sub>SO<sub>4</sub> and more diethyl ether (40 mL) were added, and the mixture was stirred for 30 minutes, then filtered through celite. After concentration, the residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> and Na<sub>2</sub>SO<sub>4</sub> was added, and the mixture was filtered and concentrated to provide the title compound.

## Example 287B

5-chloro-6-((4,4-difluorocyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 287A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 287C

N-([5-chloro-6-[(4,4-difluorocyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 287B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.46 (d, 1H), 8.14 (d, 1H), 8.00 (d, 1H), 7.56 (d, 1H), 7.47 (m, 2H), 7.35 (d, 2H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.25 (d, 2H), 3.07 (br m, 4H), 2.82 (br s, 2H), 2.30 (br m, 4H), 2.16 (br m, 2H), 2.00, 1.95, 1.85 (all m, total 9H), 1.40 (t, 2H), 1.37 (m, 2H), 0.92 (s, 6H).

## Example 288

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-([6-[[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy]-5-(trifluoromethyl)pyridin-3-yl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 288A

5-Nitro-3-(trifluoromethyl)pyridin-2-ol

3-(Trifluoromethyl)pyridin-2-ol (2.3 g) was added to concentrated sulfuric acid (15 mL) at 0° C. The mixture was

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stirred at 0° C. for 5 minutes. To this solution was added fuming nitric acid (6 mL) dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 2 hours, and then heated at 50° C. for 3 hours. After cooling, the reaction mixture was poured onto ice (200 g), and the mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide the title compound.

## Example 288B

## 2-Chloro-5-nitro-3-(trifluoromethyl)pyridine

A mixture of EXAMPLE 288A (1.69 g), phosphorus pentachloride (2.03 g), and phosphoryl trichloride (0.97 mL) was heated at 90° C. for 3 hours. After cooling, the reaction mixture was poured into ice, and extracted with ethyl acetate three times. The extract was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 10% ethyl acetate in hexanes to provide the title compound.

## Example 288C

## 6-Chloro-5-(trifluoromethyl)pyridin-3-amine

A mixture of iron (1.5 g) and ammonium chloride (2.38 g) in water (40 mL) was stirred at room temperature for 5 minutes. To this suspension was added EXAMPLE 288B in methanol (40 mL). The reaction mixture was stirred at room temperature for 1 hour. More iron (1.8 g) was added to the reaction mixture, and it was stirred for another 3 hours. The solid from the reaction mixture was filtered off, and the filtrate was partitioned between water and ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 20% ethyl acetate in hexanes to provide the title compound.

## Example 288D

## 6-chloro-5-(trifluoromethyl)pyridine-3-sulfonyl chloride

Under ice-cooling, thionyl chloride (4 mL) was added dropwise over 20 minutes to water (27 mL). The mixture was stirred overnight for 12 hours to give a SO<sub>2</sub> containing solution. Separately, EXAMPLE 288C (1.14 g) in dioxane (5 mL) was added to concentrated HCl (20 mL) at 0° C. The solution was stirred for 5 minutes. To this suspension/solution was added sodium nitrite (0.44 g) in water (6 mL) dropwise at 0° C. The solution was stirred at 0° C. for 3 hours. During this time, any solid formed was crushed with a glass rod to make sure that EXAMPLE 288C was completely reacted. To the SO<sub>2</sub> containing solution was added copper(I) chloride (0.115 g). Then, to this solution was added the diazotized EXAMPLE 288C at 0° C. The solution was stirred for 30 minutes. The reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexanes to provide the title compound.

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## Example 288E

## 6-chloro-5-(trifluoromethyl)pyridine-3-sulfonamide

EXAMPLE 288D (2.03 g) in dioxane (20 mL) solution was cooled to 0° C. Ammonium hydroxide solution was added dropwise. The reaction mixture was stirred at 0° C. for 2 hours followed by room temperature over night. The solvent was partially removed, and the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 0-3% methanol in dichloromethane to afford the title compound.

## Example 288F

## tert-butyl 4-fluoro-4-((5-sulfamoyl-3-(trifluoromethyl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 322A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 288G

## 6-((4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288F for tert-butyl(4-(1,3-difluoropropan-2-yl)morpholin-2-yl)methylcarbamate in EXAMPLE 252B.

## Example 288H

## 6-((1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting 1,3-difluoropropan-2-one for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 288G for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A.

## Example 288I

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[6-{[1-(1,3-difluoropropan-2-yl)-4-fluoropiperidin-4-yl]methoxy}-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 288H for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.50 (s, 1H), 8.57 (s, 1H), 8.27 (d, 1H), 7.91 (d, 1H), 7.58 (d, 1H), 7.40 (m, 1H), 7.35 (d, 2H), 7.28 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.29 (dd, 1H), 6.24 (d, 1H), 4.67 (d, 2H), 4.55 (d, 2H), 4.50 (s, 1H), 4.44 (s, 1H), 3.06 (m, 5H), 2.73 (m, 6H), 2.19 (d, 6H), 1.90 (m, 7H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 289

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydro furan-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 289A

5-chloro-6-(2-(tetrahydrofuran-2-yl)ethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting 2-(tetrahydro-2H-pyran-4-yl)ethanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in Example 36B.

## Example 289B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-chloro-6-[2-(tetrahydro furan-2-yl)ethoxy]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 289A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.52 (d, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.50-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.39-4.51 (m, 4H), 3.87-3.94 (m, 1H), 3.73-3.78 (m, 1H), 3.57-3.62 (m, 1H), 3.11 (s, 4H), 2.89 (s, 2H), 2.33 (s, 4H), 2.15 (s, 2H), 1.77-2.01 (m, 7H), 1.45-1.54 (m, 1H), 1.40 (t, 2H), 0.93 (s, 6H).

## Example 290

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 290A

2-chloro-4,4-dimethylcyclohex-1-enecarbaldehyde

Into a 250 ml round-bottomed flask was added N,N-dimethylformamide (3.5 mL) in dichloromethane (30 mL). The mixture was cooled to -10° C., and phosphoryl trichloride (4 mL) was added dropwise. The solution was warmed up to room temperature and 3,3-dimethylcyclohexanone (5.5 mL) was added slowly. The mixture was heated to reflux overnight. The reaction mixture was quenched by 0° C. solution of sodium acetate (25 g in 50 mL water). The aqueous layer was extracted with ether (3×200 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and dried under vacuum.

## Example 290B

2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarbaldehyde

Into a 1 L round-bottomed flask was added EXAMPLE 290A (6.8 g), 4-chlorophenylboronic acid (6.5 g) and palla-

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dium(II) acetate (0.2 g) in water (100 mL) to give a suspension. Potassium carbonate (15 g) and tetrabutylammonium bromide (10 g) were added. After degassing after subjecting to vacuum and nitrogen, the mixture was stirred at 45° C. for 4 hours. After filtering through silica gel, diethyl ether (4×200 mL) was used to extract the product. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated and purified by flash chromatography on silica with 0-10% ethyl acetate in hexanes to provide the title compound.

## Example 290C

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazine-1-carboxylate

To a solution of tert-butyl 3-methylpiperazine-1-carboxylate (0.256 g) and EXAMPLE 290B (0.350 g) in dichloromethane (2 mL) was added sodium triacetoxyborohydride (0.406 g) and the reaction was stirred at room temperature overnight. The reaction was quenched with NaHCO<sub>3</sub> solution (50 mL) and extracted with dichloromethane (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.5% to 2.5% methanol/dichloromethane gave the title compound.

## Example 290D

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-2-methylpiperazine

A solution of EXAMPLE 290C (0.298 g) and HCl (4.0M in dioxane, 2 mL) were stirred for 1 hour. The reaction was concentrated and partitioned between dichloromethane (100 mL) and NaHCO<sub>3</sub> (100 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated to provide the title compound.

## Example 290E

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 290D for EXAMPLE 3E in EXAMPLE 3I.

## Example 290F

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)-3-methylpiperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 290E for EXAMPLE 15G in EXAMPLE 15H.

## Example 290G

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-3-methylpiperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 290F for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H

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NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.66 (s, 1H), 11.54-11.30 (m, 1H), 8.62-8.53 (m, 2H), 8.03 (d, 1H), 7.78 (d, 1H), 7.48 (d, 3H), 7.34 (d, 2H), 7.06 (t, 3H), 6.68 (d, 1H), 6.38 (dd, 1H), 6.21 (s, 1H), 3.84 (d, 2H), 3.23 (s, 4H), 2.75 (s, 4H), 1.64 (s, 8H), 1.62 (d, 2H), 1.42-1.17 (m, 6H), 0.92 (s, 6H), 0.87 (s, 3H).

## Example 291

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 291A

tert-butyl 2-cyanoethyl(cyclopropyl)carbamate

To a solution of 3-(cyclopropylamino)propanenitrile (5.0 g) in tetrahydrofuran (30 mL) was added di-tert-butyl dicarbonate (9.91 g) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with 5% aqueous HCl, water and brine. After drying over  $\text{Na}_2\text{SO}_4$ , the mixture was filtered, and the solvent was evaporated under vacuum to provide the title compound.

## Example 291B

tert-butyl 3-aminopropyl(cyclopropyl)carbamate

Example 291A (9.75 g) and 7M  $\text{NH}_3$ -methanol (25 mL) were added to a Ra-Ni 2800, water slurry (19.50 g, 332 mmol) in a 250 mL pressure bottle and stirred for 2 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and evaporation of the solvent gave the title compound.

## Example 291C

tert-butyl cyclopropyl(3-(2-nitro-4-sulfamoylphenylamino)propyl)carbamate

To a solution of 4-chloro-3-nitrobenzenesulfonamide (2.5 g), and EXAMPLE 291B (2.26 g) in dioxane (20 mL) was added N,N-diisopropylethylamine (5 mL). The mixture was stirred at reflux overnight. The mixture was diluted with ethyl acetate (400 mL) and washed with water and brine. After drying over  $\text{Na}_2\text{SO}_4$ , the mixture was filtered, and the solvent was evaporated under vacuum to provide the title compound.

## Example 291D

tert-butyl 3-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenylamino)propyl(cyclopropyl)carbamate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 291C for EXAMPLE 1F in EXAMPLE 1G.

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## Example 291E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[3-(cyclopropylamino)propyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 291D (2.56 g) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 2 hours. The mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (300 mL) and washed with aqueous  $\text{NaHCO}_3$ , water, and brine and dried over  $\text{Na}_2\text{SO}_4$ . Filtration and evaporation of the solvent gave the crude product. The title compound was obtained by dissolving 200 mg of the crude material in dimethylsulfoxide/methanol (1:1, 10 mL) and loaded on Gilson, C18(100A) 250x121.2 mm (10 micron), eluting with 30% acetonitrile to 65% acetonitrile over 40 minutes.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.54 (s, 1H), 8.43 (m, 2H), 7.94 (d, 1H), 7.71 (dd, 1H), 7.57 (d, 1H), 7.43 (m, 1H), 7.34 (m, 3H), 7.05 (d, 2H), 6.90 (d, 1H), 6.63 (dd, 1H), 6.29 (d, 2H), 3.43 (m, 2H), 2.96 (m, 6H), 2.73 (m, 2H), 2.22 (m, 7H), 1.87 (m, 4H), 1.38 (m, 3H), 0.94 (m, 6H), 0.62 (m, 4H).

## Example 292

N-{[5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 292A

5-chloro-6-(2-methoxyethoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and 2-methoxyethanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 292B

N-{[5-chloro-6-(2-methoxyethoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 292A for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (400 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.63 (s, 1H), 8.48 (d, 1H), 8.17 (d, 1H), 8.01 (d, 1H), 7.56 (d, 1H), 7.49 (m, 2H), 7.35 (d, 2H), 7.04 (d, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.21 (d, 1H), 4.52 (m, 2H), 3.70 (m, 2H), 3.28 (s, 3H), 3.13 (br m, 4H), 2.88 (br s, 2H), 2.34 (br m, 4H), 2.16 (br m, 2H), 1.97 (s, 2H), 1.40 (t, 2H), 0.92 (s, 6H).



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## Example 293

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 293A

The title compound was prepared by substituting 5-bromo-2,3-difluoropyridine for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 293B

tert-butyl 5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridin-3-ylcarbamate

The title compound was prepared by substituting EXAMPLE 293A for EXAMPLE 248A in EXAMPLE 248B.

## Example 293C

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonyl chloride

The title compound was prepared by substituting EXAMPLE 293B for EXAMPLE 248B in EXAMPLE 248C.

## Example 293D

5-fluoro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 293C for EXAMPLE 248C in EXAMPLE 248D.

## Example 293E

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-fluoro-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridin-3-yl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 293D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.05 (d, 1H), 8.44 (dd, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.76 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 4.21 (d, 2H), 3.96 (dd, 2H), 3.31 (td,

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2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (m, 3H), 1.58 (dd, 2H), 1.38 (m, 4H), 0.94 (s, 6H).

## Example 294

N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 294A

tert-butyl 4-((2-chloro-4-sulfamoylphenoxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting tert-butyl-4-(hydroxymethyl)piperidine-1-carboxylate for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

## Example 294B

tert-butyl 4-((4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-chlorophenoxy)methyl)piperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 294A for EXAMPLE 1F in EXAMPLE 1G.

## Example 294C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(3-chloro-4-(piperidin-4-ylmethoxy)phenyl)sulfonyl]-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

To EXAMPLE 294B (0.286 g) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the reaction stirred at room temperature. After 3 hours the reaction was concentrated to provide the title compound.

## Example 294D

N-[(3-chloro-4-{[1-(methoxyacetyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To EXAMPLE 294C (0.75 g) as a solution in dichloromethane (1 mL) was added N,N-diisopropylethylamine (0.055 mL) followed by 2-methoxyacetyl chloride (6 μL). After stirring for 10 minutes the reaction was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.5% to 3.5% methanol/dichloromethane over 30 minutes (flow=40 mL/minutes) to provide the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.55-11.24 (m, 1H), 8.06 (d, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.57 (s, 1H), 7.51 (s, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.21 (d, 1H), 7.04 (d, 2H), 6.67 (d, 1H), 6.42 (dd, 1H), 6.18 (s, 1H), 4.42-4.32 (m, 1H), 4.03 (dd, 4H), 3.86-3.74 (m, 1H), 3.28 (s,

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3H), 3.07 (s, 5H), 2.77 (s, 3H), 2.30-1.92 (m, 9H), 1.77 (s, 2H), 1.31 (d, 4H), 0.92 (s, 6H).

## Example 295

N-[(3-chloro-4-{[1-(N,N-dimethylglycyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-{4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 2-(dimethylamino)acetyl chloride for 2-methoxyacetyl chloride in EXAMPLE 294D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 10.35-9.94 (m, 1H), 7.96 (d, 1H), 7.74 (d, 1H), 7.55 (d, 2H), 7.45 (s, 1H), 7.41-7.29 (m, 3H), 7.05 (d, 3H), 6.63 (d, 1H), 6.37-6.32 (m, 1H), 6.22 (d, 1H), 4.39 (d, 1H), 3.94 (s, 6H), 3.01 (s, 6H), 2.73 (m, 4H), 2.55 (m, 5H), 2.19 (s, 6H), 1.95 (m, 2H), 1.82 (m, 2H), 1.38 (s, 4H), 0.93 (s, 6H).

## Example 296

4-{4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 296A

tert-butyl 4-((4,4-dimethyl-2-oxocyclohexyl)methyl)piperidine-1-carboxylate

3,3-Dimethylcyclohexanone (5.60 mL) was added to sodium bis(trimethylsilyl)amide (45.3 mL, 1M in tetrahydrofuran), and the reaction was stirred for 1 hour. tert-Butyl 4-(bromomethyl)piperidine-1-carboxylate (11.1 g) in dimethylsulfoxide (30 mL) was added, and the reaction was stirred at 50° C. for 24 hours. The reaction was cooled, poured into water (300 mL), extracted three times with ether, and the combined extracts were washed three times with water, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 5-20% ethyl acetate in hexanes to provide the title compound.

## Example 296B

tert-butyl 4-((2-(4-chlorophenyl)-2-hydroxy-4,4-dimethylcyclohexyl)methyl)piperidine-1-carboxylate

(4-Chlorophenyl)magnesium bromide (14.1 mL, 1M in ether) was added to EXAMPLE 296A (3.25 g) in tetrahydrofuran (40 mL) at -78° C., and the reaction was stirred for 20 minutes, and then allowed to warm to room temperature overnight. The reaction was quenched with pH 7 buffer (20 mL), extracted with 2× ether, and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was chromatographed on silica gel using 1-20% ethyl acetate in hexanes to provide the title compound.

## Example 296C

trans-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidine

The title compound was prepared by substituting EXAMPLE 296B for EXAMPLE 1A in EXAMPLE 1B.

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## Example 296D

Trans-methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 296C for EXAMPLE 263G in EXAMPLE 263H.

## Example 296E

Trans-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohexyl)methyl)piperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 296D for EXAMPLE 3I in EXAMPLE 3J.

## Example 296F

Trans-4-{4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohexyl]methyl}piperidin-1-yl)-N-{[3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 296E for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.36 (br s, 1H), 8.60 (t, 1H), 8.55 (d, 1H), 8.03 (d, 1H), 7.78 (dd, 1H), 7.52 (m, 3H), 7.27 (d, 2H), 7.16 (d, 2H), 7.09 (m, 1H), 6.63 (dd, 1H), 6.38 (dd, 1H), 6.11 (d, 1H), 3.83 (dd, 2H), 3.52 (m, 2H), 3.26 (m, 4H), 2.61 (m, 2H), 2.35 (m, 1H), 1.89 (m, 2H), 1.76 (m, 1H), 1.62 (m, 2H), 1.38 (m, 4H), 1.25 (m, 6H), 1.12 (m, 2H), 0.95 (m, 2H), 0.94 (s, 3H), 0.88 (s, 3H).

## Example 297

4-{4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}benzamide

## Example 297A

6-((tetrahydro-2H-pyran-4-yl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 297B

4-{4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-{[6-(tetrahydro-2H-pyran-4-ylmethoxy)-5-(trifluoromethyl)pyridin-3-yl]sulfonyl}benzamide

The title compound was prepared by substituting EXAMPLE 297A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.49 (s, 1H), 8.56 (d, 1H), 8.23 (d, 1H), 7.90 (d, 1H), 7.58 (d, 1H), 7.40 (m, 1H), 7.34 (m, 2H), 7.26 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H),

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6.28 (dd, 1H), 6.24 (d, 1H), 4.24 (d, 2H), 3.86 (dd, 2H), 3.30 (m, 4H), 3.00 (s, 4H), 2.73 (s, 2H), 2.16 (m, 6H), 1.97 (m, 2H), 1.61 (dd, 2H), 1.33 (m, 4H), 0.93 (s, 6H).

## Example 298

N-({5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 298A

6-((trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methoxy)-5-chloropyridine-3-sulfonamide

The title compound was prepared by substituting (trans-4-(tert-butyldimethylsilyloxy)cyclohexyl)methanol for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

## Example 298B

N-({5-chloro-6-[(trans-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 298A for EXAMPLE 11B in EXAMPLE 11D. After the reaction was over, the solvent was removed, and the residue was treated with 1:1 trifluoroacetic acid/dichloromethane for two hours. The solvents were removed, and the residue was purified by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 $\mu$ , C18(2), 250 $\times$ 21.20 mm, 5  $\text{\AA}$ ) eluting with 20-80% acetonitrile in water with 0.1% trifluoroacetic acid to provide the title compound. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>)  $\delta$  11.65 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 8.01 (d, 1H), 7.54 (d, 1H), 7.48-7.49 (m, 1H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.21 (s, 1H), 4.53 (t, 1H), 4.18 (d, 2H), 3.08 (s, 4H), 2.84 (s, 2H), 2.29 (s, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.79-1.83 (m, 5H), 1.39 (t, 2H), 1.08-1.13 (m, 5H), 0.93 (s, 6H).

## Example 299

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 299A

3-cyano-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 284A.

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## Example 299B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-cyano-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 299A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>)  $\delta$  11.72 (s, 1H), 10.24-9.27 (m, 1H), 8.21 (d, 1H), 8.12 (dd, 1H), 8.05 (d, 1H), 7.63-7.46 (m, 3H), 7.45-7.31 (m, 3H), 7.07 (d, 2H), 6.70 (dd, 1H), 6.42 (s, 1H), 6.23 (s, 1H), 4.38 (d, 2H), 3.91-3.73 (m, 2H), 3.68-3.51 (m, 2H), 3.22-2.96 (m, 10H), 2.31-2.12 (m, 2H), 1.99 (s, 6H), 1.43 (t, 2H), 0.93 (s, 6H).

## Example 300

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 300A

6-((trans-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 121A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 300B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(trans-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 300A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>)  $\delta$  11.50 (s, 1H), 8.56 (d, 1H), 8.23 (d, 1H), 7.90 (d, 1H), 7.58 (d, 1H), 7.40 (m, 1H), 7.35 (d, 2H), 7.27 (d, 1H), 7.05 (d, 2H), 6.61 (dd, 1H), 6.28 (dd, 1H), 6.24 (d, 1H), 4.20 (d, 2H), 3.23 (s, 3H), 3.03 (m, 5H), 2.73 (s, 2H), 2.18 (m, 6H), 1.98 (m, 5H), 1.80 (m, 3H), 1.39 (t, 2H), 1.09 (m, 4H), 0.93 (s, 6H).

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## Example 301

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 301A

6-((cis-4-methoxycyclohexyl)methoxy)-5-(trifluoromethyl)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 288E for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 121A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 301B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({6-[(cis-4-methoxycyclohexyl)methoxy]-5-(trifluoromethyl)pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 301A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.49 (m, 1H), 8.54 (m, 1H), 8.23 (d, 1H), 7.91 (d, 1H), 7.59 (d, 1H), 7.40 (m, 1H), 7.34 (m, 2H), 7.27 (d, 1H), 7.04 (d, 2H), 6.61 (dd, 1H), 6.29 (dd, 1H), 6.24 (d, 1H), 4.20 (d, 2H), 3.37 (m, 2H), 3.19 (s, 3H), 3.00 (s, 4H), 2.73 (s, 2H), 2.18 (m, 6H), 1.96 (s, 2H), 1.80 (m, 3H), 1.50 (dd, 2H), 1.37 (m, 6H), 0.93 (s, 6H).

## Example 302

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 302A

4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidine

EXAMPLE 296B (1.0 g) was stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) at 35° C. for 48 hours. The mixture was concentrated, taken up in dichloromethane (100 mL), and stirred, and saturated Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) was added slowly. The solution was separated and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

## Example 302B

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 302A for EXAMPLE 263G in EXAMPLE 263H.

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## Example 302C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperidin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 302B for EXAMPLE 3I in EXAMPLE 3J.

## Example 302D

1,1-difluoro-4-methylenecyclohexane

Butyllithium (12.32 mL, 2.5 M solution in hexanes) was added to a solution of methyltriphenylphosphonium chloride (9.63 g) in tetrahydrofuran (50 mL) at 0° C., and the reaction was stirred for 5 minutes. 4,4-Difluorocyclohexanone (3.76 g) in dioxane (150 mL) was then added, and the reaction was stirred for 30 minutes. Water (3 mL) was added, and then hexane (150 mL) was slowly added, the reaction was filtered, and the solution carried on.

## Example 302E

4,4-difluoro-1-(hydroxymethyl)cyclohexanol

To the solution from EXAMPLE 302D was added water (75 mL), then N-methylmorpholine-N-oxide (6.4 mL, 50% solution in water) and OsO<sub>4</sub> (14.2 g, 2.5 wt % solution in tert-butanol) were added, and the reaction was stirred for 96 hours at 50° C. The solution was cooled to room temperature, treated with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (100 mL) for 30 minutes, and then acidified with concentrated aqueous HCl. The solution was then extracted three times with ethyl acetate, and the organic layers were combined, washed with 1M HCl, and brine, and concentrated. The crude mixture was chromatographed on silica gel using 10-100% ethyl acetate in hexanes, and then 5% methanol in ethyl acetate to give the product.

## Example 302F

5-chloro-6-((4,4-difluoro-1-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 302E for tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 302G

N-({5-chloro-6-[(4,4-difluoro-1-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 302F for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (br s, 2H), 8.51 (s, 1H), 8.18 (s, 1H), 8.02 (d, 1H), 7.53 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.69 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.88 (s, 1H), 4.27 (s, 2H), 3.10 (m, 4H), 2.88 (m, 1H), 2.33 (m, 2H), 2.15 (m,



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4H), 1.97 (s, 2H), 1.91 (m, 2H), 1.73 (m, 4H), 1.52 (m, 1H), 1.40 (m, 2H), 1.31 (m, 1H), 0.93 (s, 3H), 0.91 (m, 2H).

## Example 303

N-[(3-chloro-4-[(trans-4-(morpholin-4-yl)cyclohexyl)methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 303A

trans-4-morpholinocyclohexyl)methanol

To tert-butyl trans-4-(hydroxymethyl)cyclohexylcarbamate (0.500 g) was added hydrogen chloride (4.0M in dioxane, 2.2 mL) and the reaction was stirred for 1 hour and concentrated. The resulting solid was dissolved in acetonitrile (4 mL) and treated with N,N-diisopropylethylamine (1.523 mL) followed by 1-bromo-2-(2-bromoethoxy)ethane (0.556 g) and heated to 60° C. After stirring overnight the reaction was concentrated, loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 1% to 10% methanol/dichloromethane over 30 minutes (flow=40 mL/min) to provide the title compound.

## Example 303B

3-chloro-4-(((1r,4r)-4-morpholinocyclohexyl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 303A for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

## Example 303C

N-[(3-chloro-4-[(trans-4-(morpholin-4-yl)cyclohexyl)methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 303B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 10.96-10.59 (m, 1H), 8.02 (d, 1H), 7.82 (d, 1H), 7.69 (s, 1H), 7.50 (dd, 3H), 7.38-7.30 (m, 2H), 7.15-6.99 (m, 3H), 6.65 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 3.91 (d, 2H), 3.64 (s, 4H), 3.04 (s, 4H), 2.73 (s, 7H), 2.18 (s, 6H), 1.93 (m, 6H), 1.80-1.65 (m, 1H), 1.32 (m, 6H), 0.92 (s, 6H).

## Example 304

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[[4-(3-[[cyclopropyl(1,3-thiazol-5-yl)methyl]amino]propyl]amino]-3-nitrophenyl]sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 291E (95 mg) in dichloromethane (2 mL) and acetic acid (0.5 mL) was added thiazole-5-carbaldehyde (13 mg) followed by sodium triacetoxyborohydride (35 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and

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washed with aqueous NaHCO<sub>3</sub>, water, and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave crude product which was dissolved in dimethylsulfoxide/methanol (6 mL, 1:1) and loaded on Gilson, C18(100A) 250×121.2 mm (10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.95 (s, 1H), 8.57 (m, 2H), 8.03 (d, 1H), 7.78 (m, 2H), 7.49 (m, 3H), 7.35 (m, 2H), 7.02 (m, 3H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 4.00 (s, 2H), 3.05 (d, 4H), 2.73 (m, 2H), 2.60 (m, 2H), 2.18 (m, 7H), 1.95 (s, 2H), 1.79 (m, 3H), 1.37 (m, 3H), 0.92 (s, 6H), 0.45 (m, 4H).

## Example 305

N-[(3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 305A

3-chloro-4-((trans-4-hydroxycyclohexyl)methoxy)benzenesulfonamide

(Trans-4-(tert-butyl dimethylsilyloxy)cyclohexyl)methanol (275 mg, prepared according to a procedures in WO 2008/124878) and 3-chloro-4-fluorobenzenesulfonamide (259 mg) in tetrahydrofuran (15 mL) were treated with sodium hydride (180 mg, 60%) overnight. The reaction was quenched with water (1 mL) and trifluoroacetic acid (4 mL) was added. The resulting mixture was stirred for 1 hour and concentrated. The residue was triturated with water and methanol to provide the title compound.

## Example 305B

N-[(3-chloro-4-[(trans-4-hydroxycyclohexyl)methoxy]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 305A in place of EXAMPLE 11B. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 11.38 (s, 1H), 8.06 (d, 1H), 7.87 (d, 1H), 7.76 (dd, 1H), 7.57 (d, 1H), 7.51-7.55 (m, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.18 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.42 (dd, 1H), 6.18 (d, 1H), 4.54 (d, 1H), 3.91 (d, 2H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.78-1.90 (m, 4H), 1.63-1.75 (m, 1H), 1.38 (t, 2H), 1.00-1.25 (m, 4H), 0.92 (s, 6H).

## Example 306

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(3-chloro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 306A

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-chlorobenzenesulfonamide for 4-chloro-3-nitrobenzene-

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sulfonamide, (tetrahydro-2H-pyran-4-yl)methanamine for 4-methylpiperazin-1-amine dihydrochloride and Hunig's base for N<sup>1</sup>,N<sup>1</sup>,N<sup>2</sup>,N<sup>2</sup>-tetramethylethane-1,2-diamine in EXAMPLE 6A.

## Example 306B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 306A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.80 (s, 1H), 11.17 (br s, 1H), 8.09 (d, 1H), 7.71 (d, 1H), 7.63 (d, 1H), 7.58 (dd, 1H), 7.53 (dd, 1H), 7.50 (d, 1H), 7.34 (d, 2H), 7.03 (d, 2H), 6.74 (d, 1H), 6.66 (dd, 1H), 6.42 (m, 1H), 6.40 (t, 1H), 6.16 (d, 1H), 3.83 (m, 2H), 3.24 (m, 2H), 3.10 (m, 2H), 3.06 (br m, 4H), 2.72 (s, 2H), 2.17 (br m, 6H), 1.95 (s, 2H), 1.83 (m, 1H), 1.59 (br m, 2H), 1.38 (t, 2H), 1.20 (ddd, 2H), 0.92 (s, 6H).

## Example 307

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 307A

4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-3-(trifluoromethyl)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-(trifluoromethyl)benzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 37C for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 307B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-(trifluoromethyl)phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 307A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 8.78 (d, 1H), 8.58 (dd, 1H), 8.42 (d, 1H), 8.09 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.43 (m, 2H), 7.16 (d, 1H), 7.06 (m, 2H), 6.74 (dd, 1H), 6.51 (m, 2H), 4.21 (d, 2H), 3.87 (m, 2H), 3.78 (td, 2H), 3.06 (m, 4H), 2.76 (s, 2H), 2.25 (t, 2H), 2.13 (m, 4H), 1.95 (m, 6H), 1.39 (t, 2H), 0.93 (s, 6H).

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## Example 308

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 308A

4-(3-(cyclopropylamino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 291C (4.14 g) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 2 hours. The mixture was concentrated under vacuum and the residue was dissolved in dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of solvent gave the title compound.

## Example 308B

4-(3-(cyclopropyl(2,2,2-trifluoroethyl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (6 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (255 mg) and N,N-diisopropylethylamine (258 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of solvent gave the title compound.

## Example 308C

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(2,2,2-trifluoroethyl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 308B for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.38 (m, 1H), 8.55 (d, 2H), 8.03 (d, 1H), 7.81 (dd, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.05 (m, 3H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.07 (m, 4H), 2.82 (m, 4H), 2.18 (m, 7H), 1.38 (m, 2H), 0.92 (s, 6H), 0.44 (m, 4H).

## Example 309

N-[(3-chloro-4-{[1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 294B (0.150 g) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL). After stirring for 1 hour the reaction was concentrated and dried under high vacuum. The residue was dissolved in dichloromethane (2 mL) and treated with sodium triacetoxymethylborohydride (0.050 g) and oxetan-3-one (0.017 g) and stirred overnight at room temperature. The reaction was quenched

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with saturated aqueous NaHCO<sub>3</sub> (20 mL) and extracted into dichloromethane (50 mL). The organic layer was separated, washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 0.5% to 5% methanol/dichloromethane over 30 minutes (flow=40 mL/min) provided the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 11.21 (s, 1H), 8.05 (d, 1H), 7.87 (d, 1H), 7.75 (dd, 1H), 7.61-7.42 (m, 3H), 7.42-7.26 (m, 2H), 7.18 (d, 1H), 7.14-6.97 (m, 2H), 6.67 (dd, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.51 (dt, 4H), 3.99 (d, 2H), 3.56-3.32 (m, 1H), 3.06 (s, 4H), 2.89-2.68 (m, 4H), 2.16 (d, 6H), 2.01-1.69 (m, 7H), 1.50-1.07 (m, 4H), 0.92 (s, 6H).

## Example 310

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 310A

3,5-difluoro-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

EXAMPLE 37C (0.423 g) in tetrahydrofuran (30 mL) was treated with NaH (60% oil dispersion) (0.480 g), stirred 20 minutes at ambient temperature, treated with 3,4,5-trifluorobenzenesulfonamide (0.633 g) and stirred 30 minutes. N,N-Dimethylacetamide (15 mL) was added to increase solubility of the reactants and stirring was continued overnight at ambient temperature. Additional NaH (60% oil dispersion) (0.480 g) and N,N-dimethylacetamide (15 mL) were added and the mixture was heated overnight at 50° C. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl solution and then partitioned between saturated aqueous NH<sub>4</sub>Cl solution and ethyl acetate. The organic layer was washed with water and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on amine functionalized silica gel with 0 to 2% methanol in CH<sub>2</sub>Cl<sub>2</sub> as the eluent. The residue was further purified by reverse phase HPLC on a C18 column using a gradient of 10-70% acetonitrile/0.1% trifluoroacetic acid in water to provide the title compound.

## Example 310B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,5-difluoro-4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 310A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.06 (s, 1H), 8.41 (d, 1H), 8.11 (m, 2H), 8.08 (d, 1H), 7.66 (m, 2H), 7.44 (m, 2H), 7.07 (m, 2H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 4.26 (d, 2H), 3.85 (dd, 1H), 3.83 (dd, 1H), 3.74 (m, 2H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.87 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

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## Example 311

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 311A

4-(3-(cyclopropyl(oxetan-3-yl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (5 mL) was added oxetan-3-one (72 mg) followed by sodium triacetoxyborohydride (318 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, evaporation of the solvent gave the crude title compound.

## Example 311B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-({3-[cyclopropyl(oxetan-3-yl)amino]propyl}amino)-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 311A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 11.37 (s, 1H), 8.68 (s, 1H), 8.54 (d, 1H), 8.02 (d, 1H), 7.79 (d, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 4.62 (m, 2H), 4.48 (t, 2H), 3.98 (m, 1H), 3.37 (m, 2H), 3.06 (m, 4H), 2.73 (d, 2H), 2.59 (m, 2H), 2.23 (m, 6H), 1.95 (s, 2H), 1.74 (m, 3H), 1.38 (t, 2H), 0.92 (s, 6H), 0.41 (m, 4H).

## Example 312

N-[(3-chloro-4-{[1-(1-methyl-L-prolyl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To EXAMPLE 294B (0.065 g) was added hydrogen chloride (4.0M in dioxane, 0.339 mL) and a few drops of methanol. After 30 minutes, the reaction was concentrated, and (S)-1-methylpyrrolidine-2-carboxylic acid (0.013 g), N<sup>1</sup>-((ethylimino)methylene)-N<sup>3</sup>,N<sup>3</sup>-dimethylpropane-1,3-diamine hydrochloride (0.026 g), suspended in dichloromethane (0.5 mL) were added followed by diisopropylethylamine (0.036 mL). The mixture stirred at room temperature. After stirring overnight, the reaction mixture was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 1% to 10% methanol (containing 1N NH<sub>3</sub>)/dichloromethane over 30 minutes (flow=40 mL/minutes) to provide the title compound. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.51 (s, 1H), 10.00-9.22 (m, 1H), 7.92 (d, 1H), 7.68 (d, 1H), 7.57 (d, 1H), 7.47 (dd, 1H), 7.44-7.38 (m, 1H), 7.38-7.31 (m, 2H), 7.29 (d, 1H), 7.12-7.01 (m, 2H), 6.90 (d, 1H), 6.61 (dd, 1H), 6.31 (dd, 1H), 6.25 (d, 1H), 5.85 (d, 1H), 4.40 (s, 1H), 3.92 (s, 4H), 3.17-2.89 (m, 8H),

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2.73 (s, 4H), 2.38 (s, 3H), 2.18 (m, 6H), 1.96 (s, 2H), 1.80 (m, 2H), 1.57 (s, 2H), 1.39 (s, 2H), 1.22 (m, 2H), 0.96 (m, 6H).

## Example 313

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 313A

3,4-difluoro-5-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was obtained as a side product in EXAMPLE 310A.

## Example 313B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3,4-difluoro-5-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 313A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 8.41 (d, 1H), 8.10 (d, 1H), 7.98 (m, 2H), 7.66 (m, 1H), 7.63 (d, 1H), 7.44 (m, 2H), 7.07 (m, 2H), 6.77 (dd, 1H), 6.54 (d, 1H), 6.48 (dd, 1H), 4.12 (d, 2H), 3.83 (m, 2H), 3.75 (m, 2H), 3.08 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.15 (m, 4H), 1.97 (s, 2H), 1.82 (m, 4H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 314

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 314A

(S)-5-chloro-6-((4-cyclopropylmorpholin-2-yl)methoxy)pyridine-3-sulfonamide

A solution of EXAMPLE 244B (250 mg), anhydrous methanol (6 mL), (1-ethoxycyclopropoxy)trimethylsilane (0.474 mL), and acetic acid (0.509 mL) was heated at 70° C. for 30 minutes. After cooling to ambient temperature, sodium cyanoborohydride (112 mg) was added and the mixture was stirred for 18 hours. Additional sodium cyanoborohydride (75 mg) was added and stirring was continued 18 hours. The reaction was concentrated and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The crude product was isolated from the dried methylene chloride layer and was purified on silica gel and

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was eluted with a 1, 2.5, 5, 10% methanol in methylene chloride step gradient to provide the title compound.

## Example 314B

N-[(5-chloro-6-{[(2S)-4-cyclopropylmorpholin-2-yl]methoxy}pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 314A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 12.98 (s, 1H), 9.09 (d, 1H), 8.69 (d, 1H), 8.41 (d, 1H), 8.11 (d, 1H), 7.66-7.64 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (m, 1H), 6.48 (m, 1H), 5.72 (br s, 1H), 4.62-4.57 (m, 1H), 4.51-4.47 (m, 1H), 3.99 (m, 1H), 3.85 (m, 1H), 3.57 (m, 1H), 3.08-3.01 (m, 5H), 2.77 (s, 2H), 2.69 (m, 1H), 2.39-2.24 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.57 (m, 1H), 1.39 (t, 2H), 0.94 (m, 6H), 0.48-0.3 (m, 4H).

## Example 315

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 3J for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.70 (s, 1H), 11.35 (br s, 1H), 8.61 (m, 1H), 8.57 (d, 1H), 8.04 (d, 1H), 7.82 (dd, 1H), 7.45-7.57 (m, 3H), 7.33 (d, 2H), 7.15 (d, 1H), 7.01 (d, 2H), 6.65 (dd, 1H), 6.40 (dd, 1H), 6.11 (d, 1H), 3.85 (dd, 2H), 3.53 (m, 2H), 3.27 (m, 4H), 2.63 (m, 2H), 2.04 (m, 2H), 1.91 (s, 2H), 1.77 (m, 2H), 1.62 (m, 4H), 1.45 (m, 2H), 1.38 (m, 2H), 1.27 (m, 1H), 1.23 (m, 4H), 0.92 (s, 6H).

## Example 316

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 316A

3-chloro-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting (tetrahydro-2H-pyran-4-yl)methanol for (4-fluoro-1-methylpiperidin-4-yl)methanol in EXAMPLE 283A.

## Example 316B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperidin-1-yl)-N-({3-chloro-4-[(tetrahydro-2H-pyran-4-yl)methoxy]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 302C for EXAMPLE 1E and EXAMPLE 316A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz,



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dimethylsulfoxide- $d_6$ )  $\delta$  11.77 (s, 1H), 11.35 (br s, 1H), 8.06 (m, 1H), 7.88 (d, 1H), 7.79 (dd, 1H), 7.58 (s, 1H), 7.53 (t, 1H), 7.46 (d, 1H), 7.34 (d, 2H), 7.22 (d, 1H), 7.01 (d, 2H), 6.66 (dd, 1H), 6.42 (dd, 1H), 6.11 (d, 1H), 3.99 (d, 2H), 3.88 (dd, 2H), 3.52 (m, 2H), 3.34 (m, 4H), 2.62 (m, 2H), 2.04 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.46 (m, 2H), 1.38 (m, 4H), 0.92 (s, 6H), 0.75 (m, 2H).

## Example 317

methyl 2-({(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

## Example 317A

methyl 2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting methyl chloroformate for methyl iodide in EXAMPLE 134B.

## Example 317B

methyl 2-({(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl)-2-nitrophenylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 317A for EXAMPLE 130C in EXAMPLE 130D.  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.00 (s, 1H), 9.26 (d, 1H), 8.84 (t, 1H), 8.43 (d, 1H), 8.35 (d, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (bs, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.29-4.03 (m, 1H), 3.89-3.70 (m, 3H), 3.71 (s, 3H), 3.55-3.38 (m, 3H), 3.07 (m, 4H), 2.96 (dt, 1H), 2.86 (dd, 1H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 318

2-({(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl)-2-nitrophenylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

## Example 318A

N-ethyl-N-methyl-2-((2-nitro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxamide

The title compound was prepared by substituting N-methyl-N-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

## Example 318B

2-({(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl}sulfamoyl)-2-nitrophenylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 318A for EXAMPLE 130C in EXAMPLE

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130D.  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.00 (s, 1H), 9.26 (d, 1H), 8.86 (t, 1H), 8.44 (d, 1H), 8.33 (dd, 1H), 8.12 (d, 1H), 7.67 (t, 1H), 7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.92-3.85 (m, 2H), 3.75 (d, 1H), 3.62 (dt, 1H), 3.55-3.48 (m, 1H), 3.45-3.39 (m, 2H), 3.21 (q, 2H), 3.07 (m, 4H), 2.99 (dt, 1H), 2.90 (dd, 1H), 2.77 (s, 2H), 2.76 (s, 3H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.06 (t, 3H), 0.93 (s, 6H).

## Example 319

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 319A

4-((4-(methylsulfonyl)morpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting methanesulfonyl chloride for methyl iodide in EXAMPLE 134B.

## Example 319B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[4-(methylsulfonyl)morpholin-2-yl]methyl}amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 319A for EXAMPLE 130C in EXAMPLE 130D.  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.00 (s, 1H), 9.25 (d, 1H), 8.84 (t, 1H), 8.43 (d, 1H), 8.32 (dd, 1H), 8.13 (d, 1H), 7.67 (t, 1H), 7.65 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.92 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.99 (m, 1H), 3.92-3.88 (m, 2H), 3.64 (m, 2H), 3.56 (m, 1H), 3.50 (m, 1H), 3.07 (m, 4H), 3.04 (s, 3H), 2.95-2.88 (m, 2H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 320

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({[3-(cyclobutyl(cyclopropyl)amino)propyl]amino)-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 320A

4-(3-(cyclobutyl(cyclopropyl)amino)propylamino)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 308A (314 mg) in dichloromethane (5 mL) was added cyclobutanone (70 mg) followed by sodium triacetoxyborohydride (318 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous

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NaHCO<sub>3</sub>, water and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, evaporation of solvent gave the title compound.

## Example 320B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({3-[cyclobutyl(cyclopropyl)amino]propyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 320A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.70 (m, 1H), 8.54 (d, 1H), 8.02 (d, 1H), 7.79 (dd, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.03 (m, 3H), 6.66 (dd, 1H), 6.38 (dd, 1H), 6.19 (d, 1H), 3.37 (q, 2H), 3.06 (m, 4H), 2.73 (s, 2H), 2.63 (m, 2H), 2.21 (m, 8H), 1.82 (m, 3H), 1.53 (m, 2H), 1.38 (t, 2H), 0.94 (m, 6H), 0.41 (m, 4H).

## Example 321

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 321A

ethyl 5,5-difluoro-2-oxocyclohexanecarboxylate

To a solution of diethyl 4,4-difluoroheptanedioate (4.3 g) in toluene (50 mL) was added potassium 2-methylpropan-2-olate (2.87 g) and the reaction stirred overnight at room temperature. The reaction was quenched with 1N aqueous HCl (100 mL) and extracted with diethyl ether (150 mL). The ether layer was washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 5% ethyl acetate/hexanes gave the title compound.

## Example 321B

ethyl 5,5-difluoro-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a solution of EXAMPLE 321A (2.37 g) in dichloromethane (40 mL) at 0° C. was added N,N-diisopropylethylamine (5.02 mL) followed by trifluoromethanesulfonic anhydride (2.33 mL) and the reaction was allowed to slowly warm to room temperature. After stirring overnight the reaction was quenched with 10 mL of water then 1N aqueous HCl (100 mL). The reaction was extracted with dichloromethane (3×75 mL), and the combined organics were washed with brine (50 mL) and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 25% ethyl acetate/hexanes gave the title compound.

## Example 321C

ethyl 2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarboxylate

A solution of EXAMPLE 321B (3.47 g), 4-chlorophenylboronic acid (1.925 g) and cesium fluoride (3.43 g) in 30 mL

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of 1,2-dimethoxyethane and 15 mL of ethanol was degassed with nitrogen for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.237 g) was added and the reaction was heated to 70° C. The reaction was diluted with ether (200 mL) and washed with 1N aqueous HCl (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 40 g) eluting with a gradient of 1% to 8% ethyl acetate/hexanes over 40 minutes gave the title compound.

## Example 321D

(2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methanol

To a solution of EXAMPLE 321C (1.84 g) in diethyl ether (25 mL) at 0° C. was added lithium aluminum hydride (1.0M, 4.28 mL). The reaction was quenched with the dropwise addition of water, then 1N aqueous HCl (50 mL) was added and the reaction diluted with diethyl ether (100 mL). The organic layer was separated, washed with brine (50 mL) dried over magnesium sulfate, filtered and concentrated to provide the title compound.

## Example 321E

2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enecarbaldehyde

To a solution of EXAMPLE 321D (1.38 g) in dichloromethane (25 mL) was added Dess-Martin periodinane (2.489 g) and the reaction stirred for 1 hour at room temperature. The reaction was quenched with 1N aqueous NaOH solution (75 mL) and the product was extracted into dichloromethane (2×100 mL). The combined organics were washed with brine (75 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveris 80 g) eluting with a gradient of 1% to 10% ethyl acetate/hexanes over 40 minutes gave the title compound.

## Example 321F

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 321E for EXAMPLE 15E in EXAMPLE 15G.

## Example 321G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-difluorocyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 321F for EXAMPLE 15G in EXAMPLE 15H.

## Example 321H

4-(4-{[2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 321G for EXAMPLE 1E and EXAMPLE 3J for

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EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.74-11.63 (m, 1H), 11.53-11.29 (m, 1H), 8.57 (d, 2H), 8.05 (d, 1H), 7.85-7.77 (m, 1H), 7.49 (d, 3H), 7.38 (d, 2H), 7.16-7.06 (m, 3H), 6.73-6.64 (m, 1H), 6.43-6.36 (m, 1H), 6.21-6.14 (m, 1H), 3.93-3.77 (m, 2H), 3.29 (d, 4H), 3.07 (s, 4H), 2.79-2.57 (m, 4H), 2.45 (dd, 2H), 2.19 (s, 6H), 1.99-1.80 (m, 1H), 1.70-1.54 (m, 2H), 1.38-1.13 (m, 2H).

## Example 322

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 322A

tert-butyl

4-fluoro-4-(hydroxymethyl)piperidine-1-carboxylate

1-Tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (2 g) was taken up in tetrahydrofuran (20 ml) and cooled in an ice bath. Lithium aluminum hydride (1.0M in dioxane, 5.09 mL) was added dropwise. The reaction was stirred at room temperature for 2 hours. The reaction was quenched with water and with 1M aqueous NaOH solution and then stirred another 1 hour at room temperature. The mixture was extracted with ethyl acetate, and the extracts were combined and washed with water and with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The crude product was used without further purification.

## Example 322B

tert-butyl 4-((2-chloro-4-sulfamoylphenoxy)methyl)-4-fluoropiperidine-1-carboxylate

The title compound was prepared by substituting EXAMPLE 322A for (tetrahydro-2H-pyran-4-yl)methanol and 3-chloro-4-fluorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 322C

3-chloro-4-((4-fluoropiperidin-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 322B for EXAMPLE 1A in EXAMPLE 1B.

## Example 322D

3-chloro-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 322C (830 mg) in tetrahydrofuran (15 mL) and acetic acid (5 mL) was added oxetan-3-one (163 mg) and MP-cyanoborohydride (2.38 mmol/g, 1.9 g). The mixture was stirred at room temperature overnight. The reaction was then filtered and the filtrate was concentrated

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under vacuum. The residue was slurried in ether and the solid product was collected by filtration.

## Example 322E

N-[(3-chloro-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 322D for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.71 (s, 1H), 8.06 (d, 1H), 7.89 (d, 1H), 7.79 (m, 1H), 7.58 (d, 1H), 7.52 (t, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.25 (d, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.42 (m, 1H), 6.18 (d, 1H), 4.55 (t, 2H), 4.44 (t, 2H), 4.24 (d, 2H), 3.44 (m, 2H), 3.07 (br s, 4H), 2.74 (m, 2H), 2.59 (m, 2H), 2.14 (m, 7H), 1.95 (m, 4H), 1.78 (m, 2H), 1.38 (t, 2H), 0.92 (s, 6H).

## Example 323

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 323A

3-chloro-4-((tetrahydrofuran-3-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting 4-fluoro-3-chlorobenzenesulfonamide for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydrofuran-3-yl)methanol for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A, except here, dimethylformamide was used in place of tetrahydrofuran and the reaction was heated at 70° C. for two days.

## Example 323B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-chloro-4-(tetrahydrofuran-3-ylmethoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 323A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.73 (s, 1H), 8.07 (d, 1H), 7.89 (d, 1H), 7.80 (dd, 1H), 7.59 (d, 1H), 7.51 (dd, 1H), 7.49 (d, 1H), 7.34 (d, 2H), 7.23 (d, 1H), 7.03 (d, 2H), 6.66 (dd, 1H), 6.42 (m, 1H), 6.19 (d, 1H), 4.07 (m, 2H), 3.80 (m, 2H), 3.68 (m, 1H), 3.56 (m, 1H), 3.10 (br m, 4H), 2.85 (br s, 2H), 2.69 (m, 1H), 2.32 (br m, 4H), 2.17 (br m, 2H), 2.02 (m, 1H), 1.96 (s, 2H), 1.69 (m, 1H), 1.40 (t, 2H), 0.92 (s, 6H).

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## Example 324

4-(4-([2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 324A

4-((trans-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 120A for EXAMPLE 39B in EXAMPLE 39C.

## Example 324B

4-(4-([2-(4-chlorophenyl)-5,5-difluorocyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 321G for EXAMPLE 1E and EXAMPLE 324A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.41 (s, 1H), 8.65-8.50 (m, 2H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.60-7.44 (m, 3H), 7.41-7.34 (m, 2H), 7.14-7.02 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.17 (d, 1H), 4.50 (d, 1H), 3.23 (t, 2H), 3.06 (s, 4H), 2.70 (d, 4H), 2.44 (s, 2H), 2.33-1.94 (m, 6H), 1.78 (dd, 4H), 1.51 (d, 2H), 1.23 (s, 2H), 1.16-0.92 (m, 2H).

## Example 325

N-([3-chloro-4-([4-fluorotetrahydro-2H-pyran-4-yl]methoxy)phenyl]sulfonyl)-4-([9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 325A

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting oxetan-3-one for 1,3-difluoropropan-2-one in EXAMPLE 265G.

## Example 325B

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 325A for EXAMPLE 15G in EXAMPLE 15H.

## Example 325C

N-([3-chloro-4-([4-fluorotetrahydro-2H-pyran-4-yl]methoxy)phenyl]sulfonyl)-4-([9-(4-chlorophenyl)-3-(oxetan-3-yl)-3-azaspiro[5.5]undec-8-en-8-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 325B for EXAMPLE 1E and EXAMPLE 286A

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for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.13 (s, 1H), 8.05 (d, 1H), 7.87 (d, 1H), 7.80-7.70 (m, 1H), 7.59-7.46 (m, 3H), 7.34 (d, 2H), 7.21 (d, 1H), 7.11-7.03 (m, 2H), 6.66 (d, 1H), 6.41 (dd, 1H), 6.18 (d, 1H), 4.50 (dd, 4H), 4.26 (d, 2H), 3.85-3.69 (m, 2H), 3.61 (d, 3H), 3.05 (s, 4H), 2.69 (s, 2H), 2.37 (s, 4H), 2.17 (s, 6H), 2.04 (s, 2H), 1.87 (d, 4H), 1.49 (d, 6H).

## Example 326

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 326A

(R)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 258E for EXAMPLE 173A in EXAMPLE 173B.

## Example 326B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(2R)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 326A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

## Example 327

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 327A

(S)-4-((4-cyclopropylmorpholin-2-yl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259E for EXAMPLE 173A in EXAMPLE 173B.

## Example 327B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-([2-(2S)-4-cyclopropylmorpholin-2-yl]methyl]amino)-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 327A for EXAMPLE 130C in EXAMPLE



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130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.44 (d, 1H), 8.34 (dd, 1H), 8.12 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.94 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.88 (d, 1H), 3.84-3.81 (m, 1H), 3.59 (dt, 1H), 3.50-3.40 (m, 2H), 3.07 (m, 4H), 2.93 (d, 1H), 2.77 (s, 2H), 2.69 (d, 1H), 2.34 (dt, 1H), 2.26 (m, 2H), 2.21 (t, 1H), 2.14 (m, 4H), 1.97 (s, 2H), 1.58 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.45-0.39 (m, 4H).

## Example 328

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 328A

## spiro[2.5]octan-5-one

To a solution of 3-ethoxycyclohex-2-enone (48.1 mL) in ether (1000 mL) was added titanium(IV) isopropoxide (110 mL) followed by addition of ethylmagnesium bromide (357 mL) at ambient temperature. The reaction mixture was stirred for 2 hours at ambient temperature and was then quenched with water (500 mL). The organic layer was separated (decanted) and the water layer was extracted with ether (3x300 mL). The combined extracts were partially concentrated to approximately 300 mL. p-Toluenesulfonic acid monohydrate (3.0 g) was added and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then washed with saturated aqueous NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was purified by fractional distillation (1st fraction b.p. 27° C. at 23 torr (not product), 2nd fraction (product) b.p. 75° C. at 8 torr).

## Example 328B

## 5-chlorospiro[2.5]oct-5-ene-6-carbaldehyde

N,N-dimethylformamide (2.1 mL) in dichloromethane (3.2 mL) at -5° C. was treated slowly with POCl<sub>3</sub> (2.33 mL) keeping the bath temperature less than 0° C. The cooling bath was removed and the mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was returned to the cooling bath and EXAMPLE 328A (2.484 g) in dichloromethane (4 mL) was added slowly to the reaction mixture. The reaction mixture was heated at 45° C. for 15 hours, cooled to room temperature and then poured into a mixture of ice and saturated aqueous sodium acetate solution. After the ice melted, the mixture was extracted with diethyl ether. The combined extracts were washed with saturated aqueous NaHCO<sub>3</sub> solution and brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed with 0 to 10% CH<sub>2</sub>Cl<sub>2</sub> in hexanes, then 25% CH<sub>2</sub>Cl<sub>2</sub> in hexanes and then 100% CH<sub>2</sub>Cl<sub>2</sub> as the eluents.

## Example 328C

## 5-(4-chlorophenyl)spiro[2.5]oct-5-ene-6-carbaldehyde

Example 328B (2.9 g), 4-chlorophenylboronic acid (2.87 g), palladium(II) acetate (0.103 g), K<sub>2</sub>CO<sub>3</sub> (5.28 g) and tetrabutylammonium bromide (4.93 g) were combined in a 100-mL round bottomed flask with water (17.0 mL). The flask was flushed with nitrogen and stirred at 45° C. for 14 hours. The

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reaction mixture was partitioned between brine and diethyl ether. The organic layer was washed with brine, dried (MgSO<sub>4</sub>), filtered through a plug of celite, concentrated and chromatographed on silica gel with 0 to 2% ethyl acetate in hexanes as the eluent.

## Example 328D

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 15F for tert-butyl piperazine carboxylate and EXAMPLE 328C for 4-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

## Example 328E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl)methyl)piperazin-1-yl)benzoic acid hydrochloride

Example 328D (0.85 g) in a mixture of tetrahydrofuran (4.8 mL), methanol (2.4 mL) and water (2.4 mL) was treated with LiOH.H<sub>2</sub>O (0.184 g) and heated overnight at 50° C. The reaction mixture was cooled to room temperature, concentrated to remove tetrahydrofuran and methanol and acidified with 1 N aqueous HCl causing precipitation of the product. The solid was collected by filtration, rinsed with water and dried overnight in a vacuum oven at 80° C. to provide the title compound.

## Example 328F

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.32 (d, 1H), 8.68 (t, 1H), 8.44 (d, 1H), 8.38 (dd, 1H), 8.10 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.43 (m, 2H), 7.10 (m, 2H), 6.91 (d, 1H), 6.75 (dd, 1H), 6.51 (m, 2H), 3.97 (dd, 2H), 3.30 (td, 2H), 3.16 (t, 2H), 3.06 (m, 4H), 2.81 (s, 2H), 2.37 (t, 2H), 2.16 (m, 4H), 2.11 (s, 2H), 1.81 (m, 1H), 1.58 (dd, 2H), 1.45 (t, 2H), 1.32 (qd, 2H), 0.38 (s, 4H).

## Example 329

N-{[5-chloro-6-({4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl}methoxy)pyridin-3-yl]sulfonyl}-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 329A

ethyl 4-(cyclopropylamino)cyclohexanecarboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (3.4 g) in dichloromethane (30 mL) was added cyclopropanamine (1.14 g) followed by sodium triacetoxymethylborohydride (4.24 g). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with 2N NaOH,

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water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 329B

ethyl 4-(cyclopropyl(oxetan-3-yl)amino)cyclohexanecarboxylate

To a solution of EXAMPLE 329A (1.05 g) in dichloromethane (10 mL) was added oxetan-3-one (0.358 g) followed by sodium triacetoxyborohydride (1.05 g). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with 2N aqueous NaOH, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 329C

(4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl)methanol

To a solution of EXAMPLE 329B (1.2 g) in tetrahydrofuran (20 mL) was added lithium aluminum hydride (0.681 g). The mixture was stirred overnight. 2N aqueous NaOH solution was added dropwise to the reaction mixture. The mixture was then diluted with ethyl acetate (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 329D

5-chloro-6-((4-(cyclopropyl(oxetan-3-yl)amino)cyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 329C (706 mg) in N,N-dimethylformamide (6 mL) was added NaH (60% in mineral oil, 300 mg). The mixture was stirred for 30 minutes, and then 5,6-dichloropyridine-3-sulfonamide (706 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent the residue was loaded on a silica gel cartridge and eluted with 5 to 10% 7N NH<sub>3</sub> in methanol in dichloromethane to provide the title compound.

## Example 329E

N-([5-chloro-6-((4-[cyclopropyl(oxetan-3-yl)amino]cyclohexyl)methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 329D for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.64 (s, 1H), 8.50 (m, 1H), 8.16 (s, 1H), 8.02 (d, 1H), 7.51 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (m, 1H), 6.21 (s, 1H), 4.70 (m, 2H), 4.43 (t, 3H), 4.19 (m, 2H), 3.12 (m, 4H), 2.84 (m, 2H), 2.19 (m, 6H), 1.96 (s, 3H), 1.77 (m, 3H), 1.38 (m, 7H), 0.93 (s, 6H), 0.44 (m, 4H).

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## Example 330

4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-N-([4-(4-cyclopropylmorpholin-2-yl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J and EXAMPLE 218A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.01 (s, 1H), 9.26 (d, 1H), 8.88 (t, 1H), 8.43 (d, 1H), 8.34 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.42 (m, 2H), 7.09 (m, 2H), 6.95 (d, 1H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.49 (dd, 1H), 3.84 (m, 2H), 3.58 (td, 1H), 3.45 (m, 2H), 3.06 (m, 4H), 2.93 (d, 1H), 2.81 (s, 2H), 2.69 (d, 1H), 2.35 (m, 3H), 2.19 (m, 5H), 2.11 (s, 2H), 1.58 (m, 1H), 1.45 (t, 2H), 0.42 (m, 8H).

## Example 331

N-([3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 331A

tert-butyl 2-((2-chloro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

To a solution of tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (0.478 g) in anhydrous N,N-dimethylformamide (5 mL) was added sodium hydride (0.280 g). The mixture was stirred at room temperature for 30 minutes, followed by addition of 3-chloro-4-fluorobenzenesulfonamide (0.419 g). The mixture was stirred at 40° C. overnight. The reaction was quenched with water (10 mL), and the mixture was adjusted to pH 7 and extracted with ethyl acetate. The crude product was purified on a silica gel column eluting with 60% ethyl acetate in hexane to provide the title compound.

## Example 331B

3-chloro-4-(morpholin-2-ylmethoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 331A for EXAMPLE 113A in EXAMPLE 134A.

## Example 331C

3-chloro-4-((4-cyclopropylmorpholin-2-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 331B for EXAMPLE 173A in EXAMPLE 173B.

## Example 331D

N-([3-chloro-4-[(4-cyclopropylmorpholin-2-yl)methoxy]phenyl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 331C for EXAMPLE 130C in EXAMPLE 130D.

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<sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.04 (s, 1H), 8.54 (d, 1H), 8.43 (d, 1H), 8.27 (dd, 1H), 8.09 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 7.05 (d, 1H), 6.75 (dd, 1H), 6.52 (d, 1H), 6.50 (m, 1H), 4.20 (dd, 1H), 4.10 (dd, 1H), 3.94 (m, 1H), 3.86 (d, 1H), 3.58 (dt, 1H), 3.06 (m, 5H), 2.77 (s, 2H), 2.69 (d, 1H), 2.40-2.20 (m, 4H), 2.14 (m, 4H), 1.97 (s, 2H), 1.60 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.41 (m, 4H).

## Example 332

N-[(3-chloro-4-[[4-(4-cyclopropylmorpholin-2-yl)methyl]amino]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 332A

tert-butyl 2-((2-chloro-4-sulfamoylphenylamino)methyl)morpholine-4-carboxylate

A solution of 3-chloro-4-fluorobenzenesulfonamide (1.0 g), tert-butyl 2-(aminomethyl)morpholine-4-carboxylate (1.135 g) and N-ethyl-N-isopropylpropan-2-amine (1.246 mL) in dimethylsulfoxide (15 mL) was stirred at 115° C. for 72 hours. The mixture was concentrated, and the residue was purified on a silica gel column eluting with 60% ethyl acetate to provide the title compound.

## Example 332B

3-chloro-4-(morpholin-2-ylmethylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 332A for EXAMPLE 113A in EXAMPLE 134A.

## Example 332C

The title compound was prepared by substituting EXAMPLE 332B for EXAMPLE 173A in EXAMPLE 173B.

## Example 332D

N-[(3-chloro-4-[[4-(4-cyclopropylmorpholin-2-yl)methyl]amino]phenyl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 332C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 8.45 (m, 2H), 8.21 (dd, 1H), 8.12 (d, 1H), 7.69 (d, 1H), 7.67 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.78 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (m, 1H), 6.37 (m, 1H), 3.84 (d, 1H), 3.77 (m, 1H), 3.54 (dt, 1H), 3.35 (m, 2H), 3.05 (m, 4H), 2.94 (d, 1H), 2.77 (s, 2H), 2.68 (d, 1H), 2.32 (dt, 1H), 2.26 (m, 2H), 2.18-2.12 (m, 5H), 1.97 (s, 2H), 1.55 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.41 (m, 4H).

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## Example 333

2-[[2-(chloro-4-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

## Example 333A

2-((2-chloro-4-sulfamoylphenylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 332B for EXAMPLE 134A and N-methyl-N-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

## Example 333B

2-[[2-(chloro-4-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]phenyl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 333A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.05 (s, 1H), 8.46 (s, 1H), 8.45 (s, 1H), 8.20 (dd, 1H), 8.10 (d, 1H), 7.69 (d, 1H), 7.67 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.79 (d, 1H), 6.73 (dd, 1H), 6.52 (dd, 1H), 6.49 (d, 1H), 6.43 (m, 1H), 3.83 (d, 2H), 3.73 (d, 1H), 3.59 (dt, 1H), 3.41-3.35 (m, 3H), 3.20 (q, 2H), 3.05 (m, 4H), 2.95 (t, 1H), 2.84 (dd, 1H), 2.76 (s, 2H), 2.73 (s, 3H), 2.25 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.04 (t, 3H), 0.94 (s, 6H).

## Example 334

(2S)-2-[[2-(3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

## Example 334A

(S)-2-((3-chloro-5-sulfamoylpyridin-2-yloxy)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 244B for EXAMPLE 134A and N-methyl-N-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

## Example 334B

(2S)-2-[[2-(3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)oxy]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 334A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 12.98 (s, 1H), 9.08 (d, 1H), 8.70 (d, 1H), 8.42 (d, 1H), 8.11 (d, 1H), 7.67 (t, 1H),

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7.64 (d, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.53 (d, 1H), 6.48 (m, 1H), 4.58 (dd, 1H), 4.47 (dd, 1H), 4.03 (m, 1H), 3.84 (m, 2H), 3.63 (dt, 1H), 3.45 (d, 1H), 3.22 (q, 2H), 3.07 (m, 4H), 3.05-2.95 (m, 2H), 2.78 (s, 3H), 2.77 (s, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.07 (t, 3H), 0.94 (s, 6H).

## Example 335

N-[(5-chloro-6-[[4-(cyclopropylmorpholin-2-yl)methyl]amino]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 335A

tert-butyl 2-((3-chloro-5-sulfamoylpyridin-2-ylamino)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and tert-butyl 2-(aminomethyl)morpholine-4-carboxylate for (tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

## Example 335B

5-chloro-6-(morpholin-2-ylmethylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 335A for EXAMPLE 113A in EXAMPLE 134A.

## Example 335C

5-chloro-6-((4-cyclopropylmorpholin-2-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 335B for EXAMPLE 173A in EXAMPLE 173B.

## Example 335D

N-[(5-chloro-6-[[4-(cyclopropylmorpholin-2-yl)methyl]amino]pyridin-3-yl)sulfonyl]-4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 335C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (s, 1H), 9.15 (d, 1H), 8.49 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.80 (t, 1H), 7.69 (d, 1H), 7.65 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.73 (dd, 1H), 6.52 (m, 1H), 6.49 (d, 1H), 3.92 (m, 1H), 3.84 (m, 2H), 3.70 (m, 1H), 3.54 (dt, 1H), 3.05 (m, 4H), 2.99 (d, 1H), 2.76 (s, 2H), 2.68 (d, 1H), 2.32 (dt, 1H), 2.25 (m, 2H), 2.12 (m, 5H), 1.97 (s, 2H), 1.53 (m, 1H), 1.39 (t, 2H), 0.93 (s, 6H), 0.40 (m, 4H).

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## Example 336

2-[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

## Example 336A

2-((3-chloro-5-sulfamoylpyridin-2-ylamino)methyl)-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 335B for EXAMPLE 134A and N-methyl-N-ethyl carbamyl chloride for methyl iodide in EXAMPLE 134B.

## Example 336B

2-[[3-chloro-5-[[4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl]pyridin-2-yl)amino]methyl]-N-ethyl-N-methylmorpholine-4-carboxamide

The title compound was prepared by substituting EXAMPLE 336A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.03 (s, 1H), 9.14 (d, 1H), 8.51 (d, 1H), 8.43 (d, 1H), 8.11 (d, 1H), 7.89 (m, 1H), 7.69 (d, 1H), 7.66 (t, 1H), 7.44 (d, 2H), 7.07 (d, 2H), 6.74 (dd, 1H), 6.51 (m, 1H), 6.48 (d, 1H), 3.96 (m, 1H), 3.90-3.70 (m, 4H), 3.59 (dt, 1H), 3.43 (d, 1H), 3.17 (q, 2H), 3.05 (m, 4H), 2.95 (dt, 1H), 2.81 (dd, 1H), 2.76 (s, 2H), 2.72 (s, 3H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 1.03 (t, 3H), 0.93 (s, 6H).

## Example 337

4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[trans-4-hydroxy-4-methylcyclohexyl]methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 337A

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycarbonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

## Example 337B

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 337A (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL)



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were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

## Example 337C

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)  
methanol

To a mixture of LiBH<sub>4</sub> (13 g), EXAMPLE 337B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

## Example 337D

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 337C (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 337E

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 337D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the product.

## Example 337F

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 337G

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 337F (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL).

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After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M aqueous NaOH (69 mL) was added, followed by 30% aqueous H<sub>2</sub>O<sub>2</sub> (8.43 mL), and the solution was stirred for 1 hour. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH<sub>2</sub>PO<sub>4</sub>. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 337H

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 337G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 337I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of EXAMPLE 337H (1.55 g), EXAMPLE 337E (2.42 g), and HK<sub>3</sub>PO<sub>4</sub> (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed three times with 1M aqueous NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 337J

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

EXAMPLE 337I (200 mg) in dioxane (10 mL) and 1M aqueous NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 337K

tert-butyl(4-hydroxy-4-methylcyclohexyl)methylcarbamate

To a vigorous stirring solution of tert-butyl(4-oxocyclohexyl)methylcarbamate (1.7 g) in tetrahydrofuran (40 mL) at -78° C. was dropwise added 1.6 M methylolithium (14.02 mL) in ether. After completion of the addition, the mixture was stirred at -78° C. for 1.2 hours and poured into a cold NH<sub>4</sub>Cl aqueous solution. The resulting mixture was extracted with dichloromethane (100 mL, three times) and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The resi-

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due was dissolved in dichloromethane and loaded onto an Analogix purification system, and it was eluted with 0-50% ethyl acetate in dichloromethane to provide the title compound.

## Example 337L

## 4-(aminomethyl)-1-methylcyclohexanol

EXAMPLE 337K (1.3 g) in dichloromethane (5 mL) at 0° C. was treated with trifluoroacetic acid (2.1 mL) and a few drops of water for 1 hour. The reaction mixture was concentrated and the residue was directly used for next step.

## Example 337M

## 4-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 337L (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 mL) was treated with triethylamine overnight. The reaction mixture, was concentrated and the residue was purified by a reverse phase chromatography, eluting with 30%-50% acetonitrile in 0.1% trifluoroacetic acid water solution to isolate the title compound.

## Example 337N

## 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[trans-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A mixture of EXAMPLE 337J (3.0 g), EXAMPLE 337M (1.98 g), N,N-dimethylpyridin-4-amine (1.93 g) and N<sup>1</sup>-((ethylimino)methylene)-N<sup>3</sup>,N<sup>3</sup>-dimethylpropane-1,3-diamine hydrochloride (1.31 g) in dichloromethane (50 mL) was stirred overnight and concentrated. The residue was purified by reverse chromatography, eluted with 40%-70% acetonitrile in 0.1% TFA water. The desired fractions were concentrated to remove acetonitrile, neutralized with NaHCO<sub>3</sub> and extracted with dichloromethane. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and dried to provide the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 8.52-8.58 (m, 2H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.53 (d, 1H), 7.47-7.52 (m, 2H), 7.30-7.37 (m, 2H), 7.07 (d, 1H), 7.01-7.06 (m, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 4.25 (s, 1H), 3.25-3.32 (m, 4H), 3.07 (s, 4H), 2.75 (s, 2H), 2.09-2.24 (m, 6H), 1.95 (s, 2H), 1.50-1.73 (m, 5H), 1.28-1.43 (m, 4H), 1.06-1.18 (m, 5H), 0.92 (s, 6H).

## Example 338

## 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl)-N-[(4-[[cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 338A

## methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycar-

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bonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoromethanesulfonic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

## Example 338B

## methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

EXAMPLE 338A (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

## Example 338C

## (2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH<sub>4</sub> (13 g), EXAMPLE 338B (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N aqueous HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

## Example 338D

## tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to EXAMPLE 338C (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

## Example 338E

## 1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

EXAMPLE 338D (1 g) was stirred in dichloromethane (10 mL), trifluoroacetic acid (10 mL), and triethylsilane (1 mL) for 1 hour. The mixture was concentrated, taken up in a mixture of dichloromethane (100 mL) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution (20 mL) and stirred for 10 minutes. The layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the product.

## Example 338F

## 5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hex-

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amethyldisilazide in tetrahydrofuran (86 mL), and after 10 minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Example 338G

## 1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of EXAMPLE 338F (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M aqueous NaOH (69 mL) was added, followed by 30% aqueous H<sub>2</sub>O<sub>2</sub> (8.43 mL), and the solution was stirred for 1 hour. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH<sub>2</sub>PO<sub>4</sub>. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Example 338H

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of EXAMPLE 338G (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Example 338I

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-ylbenzoate

A mixture of EXAMPLE 338H (1.55 g), EXAMPLE 338E (2.42 g), and HK<sub>2</sub>PO<sub>4</sub> (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed three times with 1M aqueous NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Example 338J

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-ylbenzoic acid

Example 338I (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three times

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with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

## Example 338K

## tert-butyl(4-hydroxy-4-methylcyclohexyl)methylcarbamate

To a vigorous stirring solution of tert-butyl(4-oxocyclohexyl)methylcarbamate (1.7 g) in tetrahydrofuran (40 mL) at -78° C. was dropwise added 1.6 M methylolithium (14.02 mL) in ether. After completion of the addition, the mixture was stirred at -78° C. for 1.2 hours and poured into a cold NH<sub>4</sub>Cl aqueous solution. The resulting mixture was extracted with dichloromethane (100 mL, three times) and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was dissolved in dichloromethane and loaded onto an Analogix purification system, and it was eluted with 0-50% ethyl acetate in dichloromethane to provide the title compound.

## Example 338L

## 4-(aminomethyl)-1-methylcyclohexanol

EXAMPLE 338K (1.3 g) in dichloromethane (5 mL) at 0° C. was treated with trifluoroacetic acid (2.1 mL) and a few drops of water for 1 hour. The reaction mixture was concentrated and the residue was directly used for next step.

## Example 338M

## 4-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 338L (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.1 g) in tetrahydrofuran (15 mL) was treated with triethylamine overnight. The reaction mixture was concentrated and the residue was purified by a reverse phase chromatography, eluting with 30%-50% acetonitrile in 0.1% trifluoroacetic acid water solution to isolate the title compound.

## Example 338N

## 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-((cis-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

A mixture of EXAMPLE 338J (144 mg), EXAMPLE 338M (95 mg), N,N-dimethylpyridin-4-amine (123 mg) and N<sup>1</sup>-((ethylimino)methylene)-N<sup>3</sup>,N<sup>3</sup>-dimethylpropane-1,3-diamine hydrochloride (62.7 mg) in dichloromethane (7 mL) was stirred overnight and concentrated. The residue was purified by reverse chromatography, eluted with 40%-70% acetonitrile in 0.1% TFA water. The desired fractions were concentrated, neutralized with NaHCO<sub>3</sub> and extracted with dichloromethane. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and dried to provide the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.38 (s, 1H), 8.59 (t, 1H), 8.55 (d, 1H), 8.04 (d, 1H), 7.79 (dd, 1H), 7.54 (d, 1H), 7.46-7.52 (m, 2H), 7.30-7.38 (m, 2H), 7.00-7.10 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H),

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3.95 (s, 1H), 3.25 (t, 4H), 3.07 (s, 4H), 2.75 (s, 2H), 2.10-2.26 (m, 6H), 1.95 (s, 2H), 1.29-1.62 (m, 8H), 1.16-1.30 (m, 2H), 1.08 (s, 3H), 0.92 (s, 6H).

## Example 339

N-[(5-chloro-6-[[[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 339A

(1R,4S)-methyl spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-carboxylate

A reaction mixture of 1,4-dioxaspiro[4.4]non-6-ene (5 g), methyl acrylate (10.24 g), and hydroquinone (0.13 g) was heated at 100° C. in acetonitrile (12 mL) for three days. After cooling, the solvent was removed, and residue was purified by flash chromatography on silica gel eluting with 4:1 hexane/ethyl acetate to provide the title compound as a mixture of two isomers.

## Example 339B

(1R,4S)-spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-5-ylmethanol

EXAMPLE 339A (1.0 g) in tetrahydrofuran was cooled to 0° C. To this solution was added 1.0 N lithium aluminum hydride (2.8 mL) dropwise. The reaction mixture was stirred for 2 hours. Water (0.4 mL) was added followed by 2 N aqueous NaOH (0.2 mL). The solid was filtered off, and the filtrate was concentrated. Toluene was added, and it was then distilled to remove any trace amount of water. The title compound was used for the next reaction without further purification.

## Example 339C

5-chloro-6-(((1S,2R,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 339B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B. The two stereoisomers at the 5 position were isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 $\mu$ , C18(2), 250 $\times$ 21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% trifluoroacetic acid. The desired fractions were collected, and the solvents were removed under reduced vacuum at 60° C. During this process, a lot of solid formed. It was then partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give the title compound.

## Example 339D

5-chloro-6-(((1S,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

EXAMPLE 339C (0.44 g) in tetrahydrofuran (15 mL) was treated with 3.0 M methylmagnesium bromide (5.3 mL) at 0°

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C. The solution was stirred for 16 hours. The reaction mixture was then partitioned between ethyl acetate and 0.05 N aqueous HCl (20 mL). The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate in hexanes to provide the title compound.

## Example 339E

N-[(5-chloro-6-[[[(1R,2R,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 339D for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>)  $\delta$  11.66 (s, 1H), 8.50 (s, 1H), 8.16 (s, 1H), 8.02 (d, 1H), 7.49-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.20 (s, 1H), 4.40-4.48 (m, 2H), 4.31 (s, 1H), 3.09 (s, 4H), 2.83 (s, 2H), 2.15-2.33 (m, 7H), 1.96 (s, 2H), 1.87 (d, 1H), 1.65-1.69 (m, 1H), 1.54-1.56 (m, 2H), 1.36-1.47 (m, 6H), 1.26-1.30 (m, 1H), 1.19 (s, 3H), 0.93 (s, 6H).

## Example 340

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[2-(cyanoethyl)(cyclopropyl)amino]cyclohexyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 340A

4-(1,4-dioxaspiro[4.5]decan-8-ylamino)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-3-nitrobenzenesulfonamide (1.4 g) in tetrahydrofuran (30 mL) was added 1,4-dioxaspiro[4.5]decan-8-amine (1.0 g) and diisopropylethylamine (5 mL). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 340B

N-(4-(1,4-dioxaspiro[4.5]decan-8-ylamino)-3-nitrophenylsulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

To a solution of EXAMPLE 3J (617 mg) and EXAMPLE 340A (386 mg) in dichloromethane (10 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (288 mg) and 4-(dimethylamino)pyridine (183 mg). The mixture was stirred overnight. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous



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NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 340C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-nitro-4-(4-oxo cyclohexylamino)phenylsulfonyl)benzamide

To a solution of EXAMPLE 340B (386 mg) in acetone (10 mL) and water (5 mL) was added para-toluenesulfonic acid monohydrate (50 mg). The mixture was stirred at 120° C. in a Biotage Initiator microwave reactor for 30 minutes. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 340D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-(2-cyanoethyl)(cyclopropyl)amino]cyclohexyl)amino-3-nitrophenyl]sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a solution of EXAMPLE 340C (240 mg) and 3-(cyclopropylamino)propanenitrile (62 mg) in tetrahydrofuran (10 mL) was added acetic acid (2 mL) and MP-cyanoborohydride (300 mg, 2.15 mmol/g). The mixture was stirred overnight. The mixture was filtered and concentrated under vacuum and the residue was dissolved in dimethylsulfoxide/methanol (1:1, 10 mL) and loaded on Gilson, C18(100A) 250×121.2 mm (10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.55 (dd, 1H), 8.17 (d, 1H), 8.03 (d, 1H), 7.79 (d, 1H), 7.49 (m, 3H), 7.34 (d, 2H), 7.11 (m, 1H), 7.04 (d, 2H), 6.67 (dd, 1H), 6.38 (d, 1H), 6.19 (d, 1H), 4.01 (m, 1H), 3.56 (m, 1H), 3.06 (m, 4H), 2.88 (t, 2H), 2.65 (m, 6H), 2.19 (m, 6H), 2.00 (m, 7H), 1.51 (m, 6H), 0.92 (s, 6H), 0.42 (m, 4H).

## Example 341

N-(5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl)sulfonyl)-4-(4-([5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 341A

ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (31.8 g) in toluene (100 mL) was added ethylene glycol (36.5 mL) and p-toluenesulfonic acid monohydrate (0.426 g). The two phase mixture was stirred rapidly at ambient temperature for 72 hours. The reaction was diluted with water (900 mL) and extracted with ether (900 mL). The organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulfate. After filtration, the title compound was obtained by concentration under high vacuum.

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Example 341B

1,4-dioxaspiro[4.5]decane-8-ylmethanol

To a suspension of lithium aluminum hydride (8.19 g) in tetrahydrofuran (400 mL) was added dropwise a solution of EXAMPLE 341A (37.8 g) in tetrahydrofuran (75 mL). The mixture was then heated at reflux for 2 hours. The reaction mixture was cooled in an ice bath and quenched very slowly with water (8 mL). Then added sequentially were 4N sodium hydroxide (8 mL), ether (200 mL), water (24 mL), ether (500 mL) and anhydrous sodium sulfate (250 g). The resulting mixture was stirred rapidly for 2 hours and was filtered. The title compound was isolated by concentration of the filtrate.

## Example 341C

8-(benzyloxymethyl)-1,4-dioxaspiro[4.5]decane

To a suspension of sodium hydride (60% oil dispersion, 8.86 g) in tetrahydrofuran (170 mL) was added a solution of EXAMPLE 341B (30.52 g) in tetrahydrofuran (100 mL). This mixture was stirred for 30 minutes and benzyl bromide (24 mL) was added. After stirring for 72 hours, the reaction was quenched with saturated ammonium chloride solution (400 mL) and diluted with ether (500 mL). The layers were separated and the aqueous layer was extracted with ether (2×150 mL). The combined organics were dried over sodium sulfate, filtered and concentrated. The crude product was purified on silica gel eluting with a 0, 10, 15, 75% ethyl acetate in hexanes step gradient to provide the title compound.

## Example 341D

4-(benzyloxymethyl)cyclohexanone

To a solution of EXAMPLE 341C (43.02 g) in dioxane (500 mL) was added water (125 mL) and 2M hydrochloric acid (90 mL). The mixture was heated at 85° C. for 18 hours. Upon cooling, the reaction mixture was diluted with brine (1500 mL), saturated sodium bicarbonate solution (300 mL) and ether (1000 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified on silica gel eluting with a 5-50% ethyl acetate in hexanes step gradient to provide the title compound.

## Example 341E

trans-4-(benzyloxymethyl)-1-methylcyclohexanol

To 2,6-di-*t*-butyl-4-methylphenol (83.4 g) in toluene (1100 mL) was added 2.0M (in hexanes) trimethylaluminum (95 mL) somewhat carefully to control methane evolution and a small exotherm. The reaction mixture was stirred at ambient temperature under N<sub>2</sub> for 75 minutes and was then cooled to -77° C. A solution of EXAMPLE 341D (14 g) in toluene (15 mL) was added dropwise, keeping the temperature below -74° C. Methylolithium (1.6M in diethyl ether, 120 mL) was then added dropwise, keeping the temperature below -65° C. The resulting mixture was stirred at -77° C. under N<sub>2</sub> for 2 hours. The reaction mixture was then poured into 1N aqueous HCl (1600 mL), rinsing the flask with toluene. The organic layer was washed with brine and the combined aqueous layers were extracted with diethyl ether. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The concentrate was chromatographed on 650 g of spherical silica gel

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using 2.5 L of 80/20 hexanes/ethyl acetate, then 3.0 L of 75/25 hexanes/ethyl acetate, and finally 4.0 L of 70/30 hexanes/ethyl acetate as the eluents to provide the title compound.

## Example 341F

Trans-4-(hydroxymethyl)-1-methylcyclohexanol

EXAMPLE 341E (12.6 g) and ethanol (120 ml) were added to 20% Pd(OH)<sub>2</sub>/C, wet (1.260 g) in a 500 mL SS pressure bottle. The reaction mixture was stirred at ambient temperature under 30 psi hydrogen gas. Hydrogen uptake ceased at 5 minutes. The mixture was filtered through a nylon membrane rinsing with ethanol. The filtrate was concentrated and then azeotroped with toluene (100 mL) to remove any remaining ethanol. The concentrate was dried under high vacuum for 40 minutes to provide the title compound.

## Example 341G

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 40A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 341F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 341H

N-({5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridin-3-yl}sulfonyl)-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J and EXAMPLE 341G for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.09 (s, 1H), 9.18 (d, 1H), 8.74 (d, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.67 (m, 2H), 7.42 (m, 2H), 7.09 (m, 2H), 6.74 (dd, 1H), 6.52 (dd, 1H), 6.49 (d, 1H), 4.29 (d, 2H), 3.05 (m, 4H), 2.80 (s, 2H), 2.37 (t, 2H), 2.15 (m, 4H), 2.11 (s, 2H), 1.89 (m, 6H), 1.75 (m, 2H), 1.45 (t, 2H), 1.41 (s, 3H), 1.32 (m, 2H), 0.37 (m, 4H).

## Example 342

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 342A

methyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-6-carboxylate

To a 50 ml pressure bottle were placed methyl imidazo[1,2-a]pyridine-6-carboxylate (0.26 g), acetic acid (10 ml), and wet 5% palladium on carbon (0.052 g). The reaction mixture was stirred for 16 hours at 30 psi and 50° C. The solid was filtered off, and the filtrate was concentrated. The residue was taken up in ethyl acetate. It was then washed with saturated sodium bicarbonate, brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chro-

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matography on silica gel using 10-100% ethyl acetate in hexanes to provide the title compound.

## Example 342B

(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methanol

The title compound was prepared by substituting EXAMPLE 342A for EXAMPLE 339A in EXAMPLE 339B.

## Example 342C

5-chloro-6-((5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 342B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

## Example 342D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[5-chloro-6-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-ylmethoxy)pyridin-3-yl}sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 342C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.54 (s, 1H), 8.36 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.58 (d, 1H), 7.41-7.44 (m, 2H), 7.2-7.36 (m, 4H), 7.05 (d, 2H), 6.63 (dd, 1H), 6.32 (dd, 1H), 6.24 (d, 1H), 4.42-4.51 (m, 1H), 4.37-4.40 (m, 1H), 4.29 (dd, 1H), 3.91 (dd, 1H), 3.03 (s, 4H), 2.90-2.95 (m, 2H), 2.77 (s, 2H), 2.51-2.52 (m, 1H), 2.07-2.23 (m, 7H), 1.96 (s, 2H), 1.76-1.82 (m, 1H), 1.65-1.69 (m, 2H), 1.54-1.56 (m, 2H), 1.39 (t, 2H), 0.93 (s, 6H).

## Example 343

N-[(5-chloro-6-((1R,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl)methoxy)pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 343A

5-chloro-6-(1S,2S,4R)-5-oxobicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was isolated as another isomer in EXAMPLE 339C.

## Example 343B

5-chloro-6-(((1S,2S,4R,5R)-5-hydroxy-5-methylbicyclo[2.2.1]heptan-2-yl)methoxy)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 343A for EXAMPLE 339B in EXAMPLE 339C.

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N-[(5-chloro-6-[[1R,2S,4R,5R]-5-hydroxy-5-methylbicyclo[2.2.1]hept-2-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 343B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.49-7.55 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.20 (d, 1H), 4.27 (s, 1H), 4.11-4.19 (m, 2H), 3.11 (s, 4H), 2.87 (s, 2H), 1.96-2.23 (m, 10H), 1.88 (d, 1H), 1.50 (dd, 1H), 1.33-1.44 (m, 2H), 1.13-1.19 (m, 4H), 0.88-0.93 (m, 8H).

**Example 344**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 344A**

4-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

Example 347A (732 mg) and 4-fluoro-3-nitrobenzenesulfonamide (1.2 g) in tetrahydrofuran (40 mL) were treated with 60% sodium hydride (1.6 g) for 3 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by a reverse phase chromatography, eluting with 30-50% CH<sub>3</sub>CN in 0.1% trifluoroacetic acid water to provide the title compound as a single enantiomer.

**Example 344B**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 344A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 8.34 (d, 1H), 8.04 (m, 2H), 7.52 (m, 3H), 7.40 (d, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.40 (m, 1H), 6.20 (d, 1H), 4.02 (d, 2H), 3.96 (s, 1H), 3.10 (br s, 4H), 2.85 (m, 2H), 2.29 (m, 3H), 2.15 (t, 2H), 1.96 (br s, 2H), 1.68 (m, 1H), 1.55 (m, 4H), 1.42 (m, 4H), 1.27 (m, 2H), 1.10 (s, 3H), 0.92 (s, 6H).

**Example 345**

N-[(5-chloro-6-[[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy]pyridin-3-yl)sulfonyl]-4-(4-{[5-(4-chlorophenyl)spiro[2.5]oct-5-en-6-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 328E for EXAMPLE 3J and EXAMPLE 277O

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for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.07 (s, 1H), 9.13 (d, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.68 (t, 1H), 7.66 (d, 1H), 7.42 (m, 2H), 7.09 (m, 2H), 6.75 (dd, 1H), 6.51 (m, 2H), 4.64 (d, 4H), 4.53 (d, 2H), 3.39 (m, 1H), 3.06 (m, 4H), 2.81 (s, 2H), 2.51 (m, 2H), 2.37 (m, 2H), 2.12 (m, 10H), 1.90 (m, 2H), 1.45 (t, 2H), 0.38 (s, 4H).

**Example 346**

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-([4-{[3,3-difluoropyrrolidin-1-yl]cyclohexyl}amino]-3-nitrophenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 3,3-difluoropyrrolidine hydrochloride for 3-(cyclopropylamino)propanenitrile in EXAMPLE 340D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.68 (s, 1H), 11.38 (m, 1H), 8.55 (m, 1H), 8.36 (d, 1H), 8.03 (d, 1H), 7.80 (m, 1H), 7.50 (m, 3H), 7.34 (d, 2H), 7.13 (d, 1H), 7.04 (d, 2H), 6.83 (m, 1H), 6.68 (m, 1H), 6.38 (d, 1H), 6.19 (s, 1H), 4.02 (s, 1H), 3.83 (m, 1H), 3.06 (m, 4H), 2.96 (m, 2H), 2.73 (m, 4H), 2.26 (m, 8H), 1.97 (m, 4H), 1.68 (m, 4H), 1.37 (m, 2H), 0.92 (s, 6H).

**Example 347**

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 347A**

4-(hydroxymethyl)-1-methylcyclohexanol

4-(Hydroxymethyl)cyclohexanone (800 mg) in tetrahydrofuran (15 mL) was treated with 3 M methylmagnesium chloride in tetrahydrofuran (6.24 mL) at 0° C. The reaction was warmed to room temperature over 2 hours and quenched with methanol and water. The resulting mixture was concentrated and the residue was suspended in ethyl acetate. The precipitates were filtered off and the filtrate was concentrated. The residue was purified by chromatography, eluting with 0-100% ethyl acetate in hexane to provide the title compound.

**Example 347B**

5-chloro-6-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

Example 347A (970 mg) and EXAMPLE 40A (1.6 g) in N,N-dimethylformamide (8 mL) were treated with sodium hydride (1.8 g, 60%) at room temperature for 2 days. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by a reverse phase chromatography, eluting with 30-45% acetonitrile in 0.1% trifluoroacetic acid water to isolate the title compound.

**Example 347C**

5-chloro-6-((cis-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared and isolated as described in Example 347B.

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## Example 347D

N-({5-chloro-6-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 347B in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.51 (d, 1H), 8.18 (d, 1H), 8.03 (d, 1H), 7.48-7.56 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.17-4.34 (m, 3H), 3.11 (s, 4H), 2.89 (s, 2H), 2.24-2.42 (m, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.66-1.82 (m, 3H), 1.55 (d, 2H), 1.31-1.44 (m, 4H), 1.12-1.27 (m, 2H), 1.10 (s, 3H), 0.93 (s, 6H).

## Example 348

N-({5-chloro-6-[(cis-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 347C in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 8.51 (d, 1H), 8.18 (d, 1H), 8.03 (d, 1H), 7.47-7.58 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.21 (d, 2H), 3.95 (s, 1H), 3.11 (s, 4H), 2.89 (s, 2H), 2.33 (d, 4H), 2.15 (s, 2H), 1.96 (s, 2H), 1.63-1.77 (m, 1H), 1.48-1.60 (m, 4H), 1.35-1.48 (m, 4H), 1.20-1.33 (m, 2H), 1.09 (s, 3H), 0.93 (s, 6H).

## Example 349

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-(4-{[2,2-difluorocyclopropyl]amino}cyclohexyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting 2,2-difluorocyclopropanamine hydrochloride for 3-(cyclopropylamino)propanenitrile in EXAMPLE 340D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 8.47 (m, 2H), 8.12 (m, 1H), 7.98 (m, 1H), 7.72 (m, 2H), 7.47 (m, 3H), 7.34 (m, 3H), 7.05 (m, 3H), 6.65 (dd, 1H), 6.35 (m, 1H), 6.22 (d, 1H), 3.54 (m, 2H), 3.08 (m, 4H), 2.74 (m, 4H), 2.25 (m, 4H), 2.01 (m, 4H), 1.38 (m, 4H), 0.92 (s, 6H).

## Example 350

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 350A

ethyl spiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-carboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (22.75 g) and pyrocatechol (14.75 g) in toluene (200 mL) was added

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catalytic amount of para-toluenesulfonic acid monohydrate and the mixture was stirred under reflux and a Dean-Stark trap overnight. The mixture was diluted with diethyl ether (600 mL) and washed with aqueous NaHCO<sub>3</sub>, water and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated under vacuum to provide the title compound.

## Example 350B

ethyl 4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-carboxylate

A solution of EXAMPLE 350A (5.25 g) in tetrahydrofuran (40 mL) was added dropwise to a solution of lithium diisopropylamide (12 mL, 2.0M in tetrahydrofuran/heptane/ethylbenzene) at 0° C. The solution was stirred at 0° C. for 30 minutes, and then was transferred by cannula to a pre-cooled (0° C.) stirring solution of N-fluorobenzenesulformimide (7.89 g) in dry tetrahydrofuran (20 mL). The reaction mixture was stirred at 0° C. for 30 minutes, and then at 20° C. for 18 hours. The reaction mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with diethyl ether (3×200 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the crude product.

## Example 350C

(4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methanol

To a solution of EXAMPLE 350B (23 g) in tetrahydrofuran (150 mL) was added lithium aluminum hydride (3.11 g). The mixture was stirred overnight. Aqueous 2N NaOH solution was added dropwise to the reaction mixture. The mixture was then diluted with ethyl acetate (600 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the crude product which was loaded on a 600 g analogies column and eluted with 10% to 20% ethyl acetate in hexane to provide the title compound.

## Example 350D

5-chloro-6-((4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350C (89 mg) in N,N-dimethylformamide (3 mL) was added NaH (65% in mineral oil, 36 mg). The mixture was stirred for 30 minutes, and then 5,6-dichloropyridine-3-sulfonamide (85 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate (100 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, the residue was loaded on a silica gel cartridge and eluted with 30% ethyl acetate in hexane to provide the title compound.

## Example 350E

5-chloro-6-((1-fluoro-4-oxocyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350D (1.6 g) and pyridinium p-toluenesulfonate (1.2 g) in acetone (10 mL) was added



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water (2 mL) and the mixture was stirred under microwave irradiation at 100° C. for 10 minutes. The mixture was diluted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 350F

## 5-chloro-6-((cis-1-fluoro-4-hydroxycyclohexyl)methoxy)pyridine-3-sulfonamide

To a solution of EXAMPLE 350E (336 mg) in tetrahydrofuran (10 mL) was added NaBH<sub>4</sub> (75 mg). The mixture was stirred for 45 minutes. The mixture was diluted with ethyl acetate (300 mL) and washed with 2N aqueous NaOH, water, and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and the solvent was evaporated to give the crude product.

## Example 350G

## N-({5-chloro-6-[(cis-1-fluoro-4-hydroxycyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 350F for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.48 (s, 1H), 8.18 (s, 1H), 8.01 (d, 1H), 7.50 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.37 (dd, 1H), 6.21 (d, 1H), 4.62 (d, 1H), 4.47 (s, 1H), 4.40 (s, 1H), 3.46 (m, 1H), 3.06 (m, 4H), 2.88 (m, 1H), 2.25 (m, 6H), 1.99 (m, 4H), 1.58 (m, 8H), 0.93 (s, 6H).

## Example 351

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[3-nitro-4-(2-oxaspiro[3.5]non-7-ylmethoxy)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 351A

## diethyl 1,4-dioxaspiro[4.5]decane-8,8-dicarboxylate

A 500 mL round-bottomed flask was charged with diisopropylamine (16 mL) and tetrahydrofuran (311 mL). The solution was cooled to -78° C. under N<sub>2</sub> and n-BuLi (2.5 M in hexanes, 44.8 mL) was added. The reaction was stirred for 30 minutes at -78° C. and ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (20 g) was added as a tetrahydrofuran solution (ca. 10 mL). The solution was stirred at -78° C. for 1 hour and ethyl chloroformate (9 mL) was added neat. After stirring at -78° C. for 10 minutes, the reaction was warmed to room temperature over 2 hours. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and was diluted with diethyl ether. The layers were separated, the aqueous layer was extracted with diethyl ether and the combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes/ethyl acetate).

## Example 351B

## 1,4-dioxaspiro[4.5]decane-8,8-diyl dimethanol

To a 1 L round-bottomed flask was added EXAMPLE 351A (26.6 g) and tetrahydrofuran (310 mL) to give a color-

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less solution. The solution was cooled to 0° C. and lithium aluminum hydride (2M in tetrahydrofuran, 62 mL) was added via syringe. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was cooled back down to 0° C. and quenched slowly with 4.7 mL water, 4.7 mL 10% aqueous NaOH and 14 mL water. The mixture was allowed to stir until salts were formed and was then filtered through a Supelco 90 mm silica gel Buchner funnel. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-80% hexanes/ethyl acetate).

## Example 351C

## 2,8,11-trioxa-dispiro[3.2.4]tridecane

1. To a 1 L round-bottomed flask was added EXAMPLE 351B (13 g) in tetrahydrofuran (321 mL). The solution was cooled to -78° C. under N<sub>2</sub> and n-BuLi (25.7 mL) was added dropwise via syringe. After addition was complete, the mixture stirred for 30 minutes and a tetrahydrofuran solution of 4-toluenesulfonyl chloride (12.25 g) was added via addition funnel. The reaction was allowed to stir overnight, and gradually warm to room temperature. The reaction mixture was cooled to -78° C. and n-BuLi (25.7 mL) was added. The mixture was warmed to room temperature and stirred for 3 hours. The reaction was quenched with sat aqueous NH<sub>4</sub>Cl and diluted with diethyl ether. The layers were separated, the aqueous layers extracted with diethyl ether and the combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-20% acetone/hexanes).

## Example 351D

## 2-oxaspiro[3.5]nonan-7-one

To a 500 mL round-bottomed flask was added EXAMPLE 351C (11 g) in 80% aqueous acetic acid (200 mL). The reaction was heated to 65° C. and stirred for about 4 hours. Most of the acetic acid and water were removed by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-65% hexanes/ethyl acetate).

## Example 351E

## 7-methylene-2-oxaspiro[3.5]nonane

To a 250 mL round-bottomed flask was added methyltriphenylphosphonium iodide (4.33 g) in tetrahydrofuran (35.7 mL) to give a suspension. The suspension was cooled to -15° C. n-BuLi (2.5 M in hexanes, 4.28 mL) was added dropwise and the mixture was stirred at -15° C. for 40 minutes and EXAMPLE 351D (1 g) was added as a tetrahydrofuran (ca. 5 mL) solution. The mixture was stirred at -15° C. for about 15 minutes and warmed to room temperature. After 1.5 hours, the reaction was complete and was quenched with saturated aqueous NH<sub>4</sub>Cl and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted (2×) with diethyl ether. The combined organics were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase chromatography (Analogix, 80 g Grace silica gel column, 0-50% hexanes/ethyl acetate).

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## Example 351F

## 2-oxaspiro[3.5]nonan-7-ylmethanol

To a 25 mL round-bottomed flask was added EXAMPLE 351E (568 mg) and EXAMPLE 351F tetrahydrofuran (4.11 mL) to give a colorless solution. 9-Borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran, 24.7 mL) was added and the reaction was allowed to stir for 2 hours at room temperature. Ethanol (11 mL) was added followed by aqueous NaOH (5M, 4.11 mL) and then hydrogen peroxide (2.1 mL) was added. The reaction was heated at 50° C. for 2 hours. The mixture was concentrated by rotary evaporation, and diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3×) and the combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 80 g Grace, 0-70% hexanes/ethyl acetate).

## Example 351 G

## 4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-3-nitrobenzenesulfonamide

EXAMPLE 351G was prepared substituting EXAMPLE 351F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 351H

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(2-oxaspiro[3.5]nonan-7-ylmethoxy)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 351G for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H) 8.34 (s, 1H) 8.03 (d, 2H) 7.45-7.57 (m, 3H) 7.30-7.40 (m, 3H) 7.04 (d, 2H) 6.67 (dd, 1H) 6.39 (dd, 1H) 6.17-6.23 (m, 1H) 4.29 (s, 2H) 4.20 (s, 2H) 4.00 (d, 2H) 3.08 (s, 4H) 2.73-2.90 (m, 2H) 2.72 (s, 1H) 2.01-2.32 (m, 6H) 1.96 (s, 2H) 1.64-1.78 (m, 4H) 1.33-1.50 (m, 6H) 0.96-1.15 (m, 2H) 0.92 (s, 6H).

## Example 352

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 352A

## 4-((trans-4-hydroxy-4-methylcyclohexyl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 341F for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

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## Example 352B

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 352A for EXAMPLE 1F and EXAMPLE 3J for EXAMPLE 1E in EXAMPLE 1G. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.31 (br s, 1H), 8.01 (m, 2H), 7.49 (m, 3H), 7.33 (m, 3H), 7.03 (m, 2H), 6.66 (dd, 1H), 6.37 (m, 1H), 6.19 (d, 1H), 4.27 (s, 1H), 4.05 (d, 2H), 3.40 (m, 2H), 3.17 (s, 1H), 3.07 (m, 3H), 2.79 (m, 1H), 2.24 (m, 3H), 2.14 (m, 2H), 1.94 (m, 2H), 1.71 (m, 3H), 1.52 (m, 2H), 1.38 (m, 4H), 1.22 (m, 2H), 1.09 (s, 3H), 0.91 (s, 6H).

## Example 353

## 4-(4-{[2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino}phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 353A

## 1,4-dioxaspiro[4.5]decane-8,8-diylbis(methylene)bis(4-methylbenzenesulfonate)

To a 500 mL round-bottomed flask was added EXAMPLE 351B (10 g) and dichloromethane (165 mL) to give a colorless solution. Triethylamine (24.1 mL) and toluene-2-sulfonyl chloride (19.8 g) were added followed by 4-dimethylaminopyridine (0.604 g). The reaction was refluxed overnight. Saturated aqueous NH<sub>4</sub>Cl was added followed by dilution with water and additional dichloromethane. The aqueous layer was extracted with dichloromethane (2×) and the combined organics were dried (MgSO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-55% hexanes/ethyl acetate).

## Example 353B

## 8,8-bis(fluoromethyl)-1,4-dioxaspiro[4.5]decane

To a 500 mL round-bottomed flask was added EXAMPLE 353A (20 g). tetra-n-Butylammonium fluoride (1M in tetrahydrofuran, 200 mL) was added and the resulting solution was refluxed for 6 days. The reaction was cooled, diluted with diethyl ether and washed with water (3×). The organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix, 0-30% hexanes/ethyl acetate).

## Example 353C

## 4,4-bis(fluoromethyl)cyclohexanone

To a 250 mL round bottom flask was added EXAMPLE 353B (1.1 g) and 80% aqueous acetic acid (50 mL). The reaction was heated at 65° C. for 3 hours, cooled and concentrated by rotary evaporation to remove most of the acetic acid

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and water. The residue was purified by regular phase flash column chromatography (Analogix, 0-50% hexanes/ethyl acetate).

## Example 353D

## 2-chloro-5,5-bis(fluoromethyl)cyclohex-1-enecarbaldehyde

To a 100 mL pear flask was added N,N-dimethylformamide (498  $\mu$ L) and dichloromethane (8.9 mL) to give a colorless solution. The solution was cooled to 0° C. and POCl<sub>3</sub> (550  $\mu$ L) was added dropwise and then the mixture was warmed to room temperature for 30 minutes. In the meantime, to a 100 mL pear shaped flask was added EXAMPLE 353C (870 mg, 5.36 mmol) in dichloromethane (8941  $\mu$ L) to give a colorless solution. The Vilsmeier reagent was then taken up in a syringe and added dropwise to the 4,4-bis(fluoromethyl)cyclohexanone (870 mg) solution at room temperature. The resulting solution was stirred overnight. The reaction was poured into saturated aqueous NaHCO<sub>3</sub> and ice, warmed to room temperature and extracted with dichloromethane (3 $\times$ 30 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated by rotary evaporation. The residue was purified by regular phase flash column chromatography (Analogix (0-60% hexanes/ethyl acetate).

## Example 353E

## 2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enecarbaldehyde

To a 20 mL vial was added EXAMPLE 353D (460 mg), 4-chlorophenylboronic acid (414 mg), potassium carbonate (762 mg), tetrabutylammonium bromide (711 mg), palladium (II) acetate (14.85 mg) and water (2450  $\mu$ L) to give a suspension which was degassed with N<sub>2</sub> for 2 minutes. The reaction was stirred at 45° C. overnight, cooled, and poured over a Supelco silica gel Buchner funnel, washing with ethyl acetate several times. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-60% hexanes/ethyl acetate).

## Example 353F

## methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

To a 20 mL vial was added EXAMPLE 353E (240 mg), EXAMPLE 15F (297 mg) and dichloromethane (4.2 mL). Sodium triacetoxyborohydride (268 mg) was added and the reaction was stirred overnight at room temperature. The reaction was loaded directly onto silica gel and purified by regular phase flash column chromatography (Analogix, 0-80% hexanes/ethyl acetate).

## Example 353G

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 353F for EXAMPLE 15G in EXAMPLE 15H.

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## Example 353H

## 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5,5-bis(fluoromethyl)cyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

EXAMPLE 353H was prepared by replacing EXAMPLE 3J with EXAMPLE 353G and EXAMPLE 11B with EXAMPLE 1F in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>)  $\delta$  11.69 (s, 1H) 11.44 (s, 1H) 8.48-8.70 (m, 1H) 8.05 (d, 2H) 7.81 (dd, 1H) 7.46-7.59 (m, 3H) 7.35 (d, 2H) 7.12 (d, 2H) 6.68 (dd, 1H) 6.40 (dd, 1H) 6.16 (d, 1H) 4.39-4.49 (m, 2H) 4.23-4.35 (m, 2H) 3.85 (dd, J=11.87, 2.71 Hz, 2H) 3.20-3.30 (m, 4H) 2.98-3.10 (m, 4H) 2.66-2.77 (m, 2H) 2.11-2.30 (m, 6H) 2.02-2.12 (m, 3H) 1.99 (s, 1H) 1.82-1.97 (m, 1H) 1.54-1.67 (m, 4H) 1.20-1.34 (m, 2H).

## Example 354

## 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 354A

## tert-butyl 2-((2-nitro-4-sulfamoylphenoxy)methyl)morpholine-4-carboxylate

The title compound was prepared by substituting tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate for tetrahydro-2H-pyran-4-yl-methanol EXAMPLE 24A.

## Example 354B

## 4-(morpholin-2-ylmethoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 354A for EXAMPLE 113A in EXAMPLE 134A.

## Example 354C

## 4-((4-cyclopropylmorpholin-2-yl)methoxy)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 354B for EXAMPLE 173A in EXAMPLE 173B.

## Example 354D

## 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-({4-[(4-cyclopropylmorpholin-2-yl)methoxy]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 354C for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>)  $\delta$  12.98 (s, 1H), 9.06 (d, 1H), 8.50 (dd, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.66 (t, 1H), 7.62 (d, 1H), 7.44 (d, 2H), 7.26 (d, 1H), 7.07 (d, 2H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.31 (dd, 1H), 4.22 (dd, 1H),

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3.92 (m, 1H), 3.83 (d, 1H), 3.56 (dt, 1H), 3.07 (m, 5H), 2.77 (s, 2H), 2.68 (d, 1H), 2.35 (m, 2H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.59 (m, 1H), 1.39 (t, 2H), 0.94 (s, 6H), 0.40 (m, 4H).

## Example 355

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 355A

5-chloro-6-((trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

To a cooled (0° C.) solution of EXAMPLE 350E (1.2 g) in tetrahydrofuran (30 mL) was added dropwise a solution of methylmagnesium bromide (5 mL, 3.0M in ether). Upon addition, the reaction mixture solidified. More tetrahydrofuran (10 mL) was added to the mixture and stirring was continued for 1 hour. The mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The mixture was filtered and concentrated. The residue was dissolved in dimethylsulfoxide/methanol (20 mL, 1:1) and loaded on Gilson, C18(100A) 250×121.2 mm (10 micron), with 30% acetonitrile to 65% acetonitrile over 40 minutes to separate the two isomers and isolate the title compound.

## Example 355B

N-({5-chloro-6-[(trans-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 355A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.47 (s, 1H), 8.17 (s, 1H), 7.54 (d, 1H), 7.48 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.37 (d, 1H), 6.22 (d, 1H), 4.49 (s, 1H), 4.42 (s, 1H), 4.15 (s, 1H), 3.06 (m, 4H), 2.84 (m, 1H), 2.25 (m, 6H), 1.96 (s, 3H), 1.83 (m, 4H), 1.44 (m, 6H), 1.14 (s, 3H), 0.93 (s, 6H).

## Example 356

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 356A

5-chloro-6-((cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy)pyridine-3-sulfonamide

The title compound was prepared as described in EXAMPLE 355A.

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## Example 356B

N-({5-chloro-6-[(cis-1-fluoro-4-hydroxy-4-methylcyclohexyl)methoxy]pyridin-3-yl}sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 356A for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.52 (s, 1H), 8.20 (s, 1H), 8.03 (d, 1H), 7.51 (m, 3H), 7.35 (d, 2H), 7.05 (d, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.21 (d, 1H), 4.55 (s, 1H), 4.48 (s, 1H), 4.34 (s, 1H), 3.08 (m, 4H), 2.89 (d, 2H), 2.27 (m, 5H), 1.93 (m, 4H), 1.66 (m, 4H), 1.43 (m, 4H), 1.11 (s, 3H), 0.93 (s, 6H).

## Example 357

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-cyano-4-{[4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 357A

## ethyl

4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

To 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.000 g) was added HCl (4.0M in dioxane, 4.54 mL). After 1 hour the reaction was concentrated and dried under high vacuum. The resulting solid was dissolved in dichloromethane (5 mL) and treated with sodium triacetoxyborohydride (1.155 g) and oxetan-3-one (0.262 g) and stirred overnight. The reaction was quenched with saturated NaHCO<sub>3</sub> solution (20 mL) and extracted into dichloromethane (2×25 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting with a gradient of 0.5% to 3.75% methanol/dichloromethane over 40 minutes (flow=30 mL/min) gave the title compound.

## Example 357B

(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

To a solution of EXAMPLE 357A (0.59 g) in tetrahydrofuran (5 mL) was added lithium aluminum hydride (1.80 mL) at 0° C. The reaction was removed from the ice bath and allowed to warm to room temperature. The reaction was quenched by the dropwise addition of 0.6 mL of water followed by 0.2 mL of 2N aqueous NaOH. The reaction was filtered through elite and rinsed with ethyl acetate (50 mL). The mixture and the residue was loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minutes (flow=40 mL/minutes) to provide the title compound.



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## Example 357C

3-cyano-4-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 357B for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 284A.

## Example 357D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-cyano-4-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 357C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.49-11.14 (m, 1H), 8.17 (d, 1H), 8.03 (d, 2H), 7.51 (dd, 3H), 7.43-7.26 (m, 3H), 7.12-6.96 (m, 2H), 6.67 (dd, 1H), 6.40 (dd, 1H), 6.20 (d, 1H), 4.55 (t, 2H), 4.45 (t, 2H), 4.34 (d, 2H), 3.49 (s, 1H), 3.09 (s, 8H), 2.39-1.66 (m, 14H), 1.39 (s, 2H), 0.92 (s, 6H).

## Example 358

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-([trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 358A

benzyl(4-ethyl-4-hydroxycyclohexyl)methylcarbamate

To a vigorous stirring solution of benzyl(4-oxocyclohexyl)methylcarbamate (1 g) in tetrahydrofuran (20 mL) at -78° C. was slowly added 1 Methylmagnesium bromide (11.48 mL, 11.48 mmol) in ether. After completion of the addition, the mixture was stirred at -78° C. for 2 hours and was warmed to 0° C., and stirred in an ice bath for 30 minutes. The reaction was quenched with a cold NH<sub>4</sub>Cl aqueous solution. The precipitates were filtered off and washed with ethyl acetate. The filtrate was concentrated. The residue was dissolved in dichloromethane and loaded onto Analogix purification system, and was eluted with 0-50% ethyl acetate in dichloromethane to provide the title compound.

## Example 358B

4-(aminomethyl)-1-ethylcyclohexanol

A mixture of EXAMPLE 358A (500 mg) and 10% Pd/C (100 mg) in tetrahydrofuran (15 mL) was stirred under H<sub>2</sub> for 3 hours. The insoluble material was removed by filtration, and the filtrate was concentrated to provide the title compound.

## Example 358C

4-((trans-4-ethyl-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 358B (270 mg) and 4-fluoro-3-nitrobenzenesulfonamide (417 mg) in tetrahydrofuran were treated with

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triethylamine (0.8 mL) overnight. The reaction was quenched with water. The resulting mixture was neutralized with diluted aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by a reverse phase chromatography, eluting with 40-55% acetonitrile in 0.1% trifluoroacetic acid water to isolate the title compound.

## Example 358D

4-((cis-4-ethyl-4-hydroxycyclohexyl)methylamino)-3-nitrobenzenesulfonamide

The title compound was prepared and isolated as described in Example 358C.

## Example 358E

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-([trans-4-ethyl-4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 358C in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.35 (s, 1H), 8.56 (d, 2H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.45-7.57 (m, 3H), 7.34 (d, 2H), 7.00-7.10 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.98 (s, 1H), 3.24-3.31 (m, 4H), 3.07 (s, 4H), 2.75 (s, 2H), 2.17 (d, 6H), 1.95 (s, 2H), 1.54-1.73 (m, 5H), 1.35-1.47 (m, 4H), 1.20-1.32 (m, 2H), 1.03-1.18 (m, 2H), 0.92 (s, 6H), 0.81 (t, 3H).

## Example 359

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(4-([cis-4-ethyl-4-hydroxycyclohexyl)methyl]amino)-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 358D in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.34 (s, 1H), 8.60 (t, 1H), 8.56 (d, 1H), 8.05 (d, 1H), 7.80 (dd, 1H), 7.54 (d, 1H), 7.47-7.52 (m, 2H), 7.34 (d, 2H), 7.01-7.10 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.77 (s, 1H), 3.26 (t, 2H), 3.07 (s, 4H), 2.76 (s, 2H), 2.10-2.26 (m, 6H), 1.95 (s, 2H), 1.46-1.61 (m, 5H), 1.28-1.46 (m, 6H), 1.12-1.24 (m, 2H), 0.92 (s, 6H), 0.82 (t, 3H).

## Example 360

4-(4-([2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 360A

ethyl  
8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

Into a 500 mL round-bottomed flask was added diisopropylamine (7.98 mL) in tetrahydrofuran (233 mL) to give a

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colorless solution. The mixture was cooled to  $-78^{\circ}\text{C}$ . under  $\text{N}_2$  and n-BuLi (2.5 M in hexanes, 22.40 mL) was added. The reaction was stirred for 30 minutes and ethyl 1,4-dioxaspiro [4.5]decane-8-carboxylate (10 g) was added. The reaction was allowed to stir for 1.5 hours upon which time  $\text{CH}_3\text{I}$  (4.38 mL) was added. The reaction was allowed to warm to room temperature overnight with stirring. Water was added and the aqueous layer was extracted with ethyl acetate. The combined organics were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated by rotary evaporation. The residue was purified by normal phase flash column chromatography (Analogix, 0-50% hexanes/ethyl acetate).

## Example 360B

(8-methyl-1,4-dioxaspiro[4.5]decane-8-yl)methanol

In a 500 mL round-bottomed flask was lithium aluminum hydride (1.772 g) in tetrahydrofuran (234 mL) to give a suspension. This suspension was cooled to  $0^{\circ}\text{C}$ . and ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (10.66 g) was added via addition funnel. The reaction was stirred overnight at room temperature and then cooled back down to  $0^{\circ}\text{C}$ . The excess lithium aluminum hydride was slowly quenched with 1.8 mL water, 1.8 mL aqueous NaOH (5N) and 5.6 mL water. The suspension was stirred until the salts turned white and was then filtered through a plug of silica gel. The filtrate was concentrated by rotary evaporation and the residue was purified by regular phase flash column chromatography (Analogix, 0-75% hexanes/ethyl acetate).

## Example 360C

8-(methoxymethyl)-8-methyl-1,4-dioxaspiro[4.5]decane

To a 250 mL round-bottomed flask was added NaH (0.902 g) and tetrahydrofuran (37.6 mL) to give a suspension. EXAMPLE 360B was added as a tetrahydrofuran solution at room temperature. The suspension was stirred for 30 minutes and then  $\text{CH}_3\text{I}$  (0.611 mL) was added. The reaction was stirred under  $\text{N}_2$  overnight, carefully quenched with brine and diluted with water and ether. The aqueous layer was extracted with ether (2x) and the combined organics were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography (Analogix, 0-60% hexanes/ethyl acetate).

## Example 360D

4-(methoxymethyl)-4-methylcyclohexanone

The title compound was prepared by substituting EXAMPLE 360C for EXAMPLE 353B in EXAMPLE 353C.

## Example 360E

2-chloro-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 360D for EXAMPLE 353C in EXAMPLE 353D.

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## Example 360F

2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enecarbaldehyde

The title compound was prepared by substituting EXAMPLE 360E for EXAMPLE 353D in EXAMPLE 353E.

## Example 360G

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 360F for EXAMPLE 353E in EXAMPLE 353F.

## Example 360H

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 360G for EXAMPLE 15G in EXAMPLE 15H.

## Example 360I

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-5-(methoxymethyl)-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenylsulfonyl)benzamide

The title compound was prepared by replacing EXAMPLE 3J with EXAMPLE 360H and EXAMPLE 11B with EXAMPLE 1F in EXAMPLE 11D.  $^1\text{H}$  NMR (300 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.68 (s, 1H) 11.43 (s, 1H) 8.45-8.72 (m, 2H) 8.04 (d, 1H) 7.80 (dd, 1H) 7.44-7.61 (m, 3H) 7.34 (d, 2H) 6.99-7.20 (m, 3H) 6.68 (dd, 1H) 6.39 (dd, 1H) 6.18 (d, 1H) 3.85 (dd, 2H) 3.25-3.30 (m, 4H) 3.24 (s, 3H) 3.02-3.17 (m, 6H) 2.72 (dd, 2H) 2.18 (s, 5H) 2.03-2.13 (m, 2H) 1.81-1.93 (m, 2H) 1.57-1.67 (m, 2H) 1.47-1.56 (m, 1H) 1.17-1.41 (m, 3H) 0.91 (s, 3H).

## Example 361

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((2S)-4-(oxetan-3-yl)morpholin-2-yl)methyl]amino)phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 361A

(S)-3-nitro-4-((4-(oxetan-3-yl)morpholin-2-yl)methylamino)benzenesulfonamide

The title compound was prepared by substituting EXAMPLE 259E for tert-butyl piperazine-1-carboxylate and 3-oxetanone for 4'-chlorobiphenyl-2-carboxaldehyde in EXAMPLE 1A.

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## Example 361B

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methoxy}phenyl)piperazin-1-yl)-N-{[3-nitro-4-  
([(2S)-4-(oxetan-3-yl)morpholin-2-yl]methyl]amino)phenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 361A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.00 (s, 1H), 9.26 (d, 1H), 8.87 (t, 1H), 8.43 (d, 1H), 8.35 (dd, 1H), 8.11 (d, 1H), 7.66 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.96 (d, 1H), 6.75 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 4.64 (m, 4H), 3.93 (m, 1H), 3.89 (d, 1H), 3.68 (dt, 1H), 3.53-3.35 (m, 3H), 3.07 (m, 4H), 2.77 (s, 2H), 2.72 (d, 1H), 2.44 (d, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.85 (t, 1H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 362

N-(3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 362A

3-chloro-4-(((1r,4r)-4-hydroxy-4-methylcyclohexyl)methoxy)benzenesulfonamide

To a solution of EXAMPLE 341F (300 mg) in N,N-dimethylformamide (10 mL) was added sodium hydride (416 mg) portionwise. The resulting suspension was stirred for 15 minutes. 3-Chloro-4-fluorobenzenesulfonamide (425 mg) was added and stirring was continued for 72 hours. The reaction was quenched with water and the pH was adjusted to ca. 7. The mixture was diluted with brine (75 mL) and extracted with methylene chloride. The crude product was isolated from the dried methylene chloride layer by concentration and was purified on silica gel eluted with a 10, 25, 50% ethyl acetate in methylene chloride step gradient to provide the title compound.

## Example 362B

N-(3-chloro-4-[(trans-4-hydroxy-4-methylcyclohexyl)methoxy]phenyl)sulfonyl)-4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 362A for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (400 MHz, pyridine-d<sub>5</sub>) δ 13.07 (m, 1H), 8.58 (d, 1H), 8.45 (d, 1H), 8.31 (dd, 1H), 8.11 (d, 1H), 7.69-7.67 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.97 (d, 1H), 6.74 (dd, 1H), 6.52 (m, 2H), 5.34 (br s, 2H), 3.82 (d, 2H), 3.06 (m, 4H), 2.77 (s, 2H), 2.25 (m, 2H), 2.13 (m, 4H), 1.97-1.85 (m, 7H), 1.82-1.73 (m, 2H), 1.44-1.32 (m, 7H), 0.94 (m, 6H).

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## Example 363

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methoxy}phenyl)piperazin-1-yl)-N-{[4-(4-{[2-(cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 363A

4-((4'-fluorospiro[benzo[d][1,3]dioxole-2,1'-cyclohexane]-4'-yl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 350C (495 mg) in N,N-dimethylformamide (6 mL) was added NaH (65% in mineral oil, 320 mg). The mixture was stirred for 30 minutes, and then 4-fluoro-3-nitrobenzenesulfonamide (457 mg) was added. The mixture was stirred overnight. The mixture was poured over aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate (300 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, the residue was loaded on a silica gel cartridge and was eluted with 30% ethyl acetate in hexane to provide the title compound.

## Example 363B

4-((1-fluoro-4-oxocyclohexyl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 363A (860 mg) in ethanol (30 mL) was added concentrated HCl (10 mL) and the mixture was stirred at 100° C. for 3 hours. The mixture was neutralized with solid Na<sub>2</sub>CO<sub>3</sub> and extracted with dichloromethane (300 mL) and washed with aqueous NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

## Example 363C

4-((4-((2-cyanoethyl)(cyclopropyl)amino)-1-fluorocyclohexyl)methoxy)-3-nitrobenzenesulfonamide

To a solution of EXAMPLE 363B (200 mg) in dichloromethane (6 mL) was added 3-(cyclopropylamino)propanenitrile (64 mg) followed by sodium triacetoxyborohydride (184 mg). The mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (400 mL) and washed with 2N aqueous NaOH, water, and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the mixture was filtered and evaporation of the solvent gave the title compound.

## Example 363D

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methoxy}phenyl)piperazin-1-yl)-N-{[4-(4-{[2-(cyanoethyl)(cyclopropyl)amino]-1-fluorocyclohexyl}methoxy)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 363C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.66 (s, 1H), 8.35 (s, 1H), 8.02 (d, 2H), 7.51 (m, 3H), 7.40 (m, 1H), 7.35 (d, 2H), 7.04 (d, 2H), 6.67

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(dd, 1H), 6.39 (d, 1H), 6.20 (s, 1H), 4.27 (d, 2H), 3.13 (m, 4H), 2.88 (m, 3H), 2.67 (m, 4H), 2.09 (m, 10H), 1.49 (m, 9H), 0.93 (s, 6H), 0.45 (m, 4H).

## Example 364

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 364A

## 6-amino-5-nitropyridine-3-sulfonic acid

6-Aminopyridine-3-sulfonic acid (20 g) in concentrated H<sub>2</sub>SO<sub>4</sub> (80 mL) was heated at 50° C. until it was completely dissolved. To this solution was added fuming HNO<sub>3</sub> slowly over 20 minutes, so the internal temperature did not exceed 55° C. After the addition was complete, the reaction mixture was heated at 50° C. for 1 hour. After it was cooled to room temperature, it was poured into 150 g of ice. The mixture was stirred for another hour. The flask was cooled to 0° C., and was kept at 0° C. for another 2 hours. The solid was collected by filtration, and washed with cold 1:1 water/ethanol (20 mL), followed by diethyl ether (10 mL). The solid was dried in a vacuum oven overnight to provide the title compound.

## Example 364B

## 6-hydroxy-5-nitropyridine-3-sulfonic acid

EXAMPLE 364A (4.0 g) in aqueous HCl (37%, 12 mL) and water (50 mL) was treated with sodium nitrite (1.19 g) in water (8 mL) dropwise at 0° C. After the addition was complete, the reaction mixture was stirred at 0° C. for 1 hour. The mixture was heated at reflux for 2 hours. Water was distilled off to give a dry residue. After the residue was cooled to room temperature, a solution of 1:1 ethano/water (20 mL) was added. The resulting suspension was cooled to 0° C., and kept at 0° C. for 1 hour. The solid was collected by filtration to provide the title compound.

## Example 364C

## 6-chloro-5-nitropyridine-3-sulfonyl chloride

A mixture of EXAMPLE 364B (2.6 g), PCl<sub>5</sub> (5.91 g), and POCl<sub>3</sub> (10 mL) was heated at 120° C. for 4 hours. The initial suspension became a clear solution. The excess of POCl<sub>3</sub> was distilled off. After it was cooled to room temperature, the residue was poured into 50 g of crushed ice. The solid was extracted into ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated to give crude product that was used in the next step without further purification.

## Example 364D

## 6-chloro-5-nitropyridine-3-sulfonamide

EXAMPLE 364C in tetrahydrofuran (10 mL) was cooled to -10° C. To this solution was added concentrated ammonium hydroxide (0.82 mL) dropwise. The solution was stirred at -10° C. for 10 minutes. The solvent was removed under

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pressure at room temperature. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 5-50% ethyl acetate in hexanes to provide the title compound.

## Example 364E

## 5-nitro-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

The title compound was prepared by substituting EXAMPLE 364D for 4-fluoro-3-nitrobenzenesulfonamide and (tetrahydro-2H-pyran-4-yl)methanamine for (4-fluoro-2H-pyran-4-yl)methanamine in EXAMPLE 138D.

## Example 364F

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({5-nitro-6-[(tetrahydro-2H-pyran-4-ylmethyl)amino]pyridin-3-yl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 364E for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 8.93 (s, 1H), 8.73 (d, 1H), 8.69 (d, 1H), 8.00 (d, 1H), 7.54 (d, 1H), 7.47-7.48 (m, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.68 (dd, 1H), 6.35 (dd, 1H), 6.22 (d, 1H), 3.83 (dd, 2H), 3.51 (t, 2H), 3.21-3.27 (m, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 1.90-2.27 (m, 12H), 1.58 (dd, 2H), 1.39 (t, 2H), 1.18-1.28 (m, 2H), 0.88-0.93 (m, 8H).

## Example 365

## 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(2-oxaspiro[3.5]non-7-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 365A

## 7-(azidomethyl)-2-oxaspiro[3.5]nonane

To a 250 mL round-bottomed flask was EXAMPLE 351F (350 mg) in tetrahydrofuran (75.0 mL) to give a colorless solution. The solution was cooled to 0° C., triphenylphosphine (2.94 g), diisopropyl azodicarboxylate (2.18 mL) and diphenyl phosphorazidate (2.32 mL) were added and the reaction was stirred for 30 minutes at room temperature. The mixture was concentrated and purified the residue by regular phase flash column chromatography (Analoxig, 0-20% hexanes/ethyl acetate).

## Example 365B

## 2-oxaspiro[3.5]nonan-7-ylmethanamine

To a 50 mL round-bottomed flask was added 10% palladium on carbon (58.7 mg). The flask was flushed with N<sub>2</sub> and EXAMPLE 365A (400 mg) was added as a methanol solution (10.5 mL). The flask was then flushed several times with H<sub>2</sub>



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(via balloon) and heated to 45° C. for 2 hours. The reaction was cooled to room temperature, filtered through celite and the filtrate was concentrated by rotary evaporation. The residue was used in the next step without further purification.

**Example 365C**

4-(2-oxaspiro[3.5]nonan-7-ylmethylamino)-3-nitrobenzenesulfonamide

The title compound was prepared by substituting EXAMPLE 365B for 1-(tetrahydropyran-4-yl)methylamine in EXAMPLE 1F.

**Example 365D**

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(4-(2-oxaspiro[3.5]nonan-7-ylmethylamino)-3-nitrophenylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 365C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H) 11.25-11.49 (m, 1H) 8.48-8.66 (m, 2H) 8.03 (d, 1H) 7.79 (dd, 1H) 7.41-7.61 (m, 3H) 7.27-7.40 (m, 2H) 7.05 (t, 3H) 6.67 (dd, 1H) 6.39 (dd, 1H) 6.18 (d, 1H) 4.29 (s, 2H) 4.19 (s, 2H) 3.17-3.27 (m, 2H) 2.99-3.14 (m, 4H) 2.69-2.79 (m, 2H) 2.09-2.28 (m, 6H) 2.04 (d, 2H) 1.95 (s, 2H) 1.66 (d, 2H) 1.49-1.61 (m, 1H) 1.29-1.45 (m, 4H) 0.93-1.05 (m, 2H) 0.92 (s, 6H).

**Example 366**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((4-cyano-4-methylcyclohexyl)methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

**Example 366A**

tert-butyl(4-cyano-4-methylcyclohexyl)methylcarbamate

To a cooled (-78° C.) solution of tert-butyl(4-cyanocyclohexyl)methylcarbamate (500 mg) in tetrahydrofuran (10 mL) was added lithium diisopropylamide (2.0 mL, 2M in heptane). The mixture was stirred at -78° C. for 30 minutes before the addition of CH<sub>3</sub>I (1 mL). The mixture was then stirred and the temperature was allowed to warm to room temperature. The reaction was quenched with aqueous NH<sub>4</sub>Cl and the mixture was extracted with ethyl acetate (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent and silica gel chromatography (40% ethyl acetate in hexane) of the crude material gave the title compound.

**Example 366B**

4-(aminomethyl)-1-methylcyclohexanecarbonitrile

To a solution of EXAMPLE 366A (480 mg) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL). The mixture was stirred for 3 hours. The mixture was then concentrated under vacuum and was used directly in the next reaction without further purification.

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4-((4-cyano-4-methylcyclohexyl)methylamino)-3-nitrobenzenesulfonamide

To a solution of 4-fluoro-3-nitrobenzenesulfonamide (362 mg) in tetrahydrofuran (10 mL) was added EXAMPLE 366B (250 mg) and N,N-diisopropylethylamine (2 mL). The mixture was stirred overnight. The mixture was diluted with ethyl acetate (300 mL) and washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the solvent gave the title compound.

**Example 366D**

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([4-((4-cyano-4-methylcyclohexyl)methyl)amino]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 3J for EXAMPLE 1E and EXAMPLE 366C for EXAMPLE 1F in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.67 (s, 1H), 11.37 (m, 1H), 8.59 (m, 2H), 8.04 (d, 1H), 7.80 (d, 1H), 7.51 (m, 3H), 7.34 (d, 2H), 7.10 (d, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (m, 1H), 6.19 (s, 1H), 3.07 (m, 4H), 2.75 (m, 2H), 2.17 (m, 7H), 1.76 (m, 9H), 1.32 (m, 9H), 0.92 (s, 6H).

**Example 367**

{[4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)amino}methyl pivalate

This example was prepared by substituting chloromethyl pivalate for chloromethyl butyrate in EXAMPLE 368. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.72 (s, 1H), 8.43 (d, 1H), 8.22 (dd, 1H), 8.01 (d, 1H), 7.55 (m, 3H), 7.36 (m, 3H), 7.03 (d, 2H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.17 (d, 1H), 5.83 (s, 2H), 4.40 (d, 2H), 3.78 (m, 2H), 3.59 (m, 2H), 3.08 (br m, 4H), 2.73 (br s, 2H), 2.18 (br m, 6H), 1.96 (s, 2H), 1.84 (m, 4H), 1.39 (m, 2H), 1.00 (s, 9H), 0.92 (s, 6H).

**Example 368**

{[4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]({4-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]-3-nitrophenyl)sulfonyl)amino}methyl butyrate

EXAMPLE 37E (500 mg) was dissolved in acetonitrile (3.7 mL) and chloromethyl butyrate (77 mg) and Hunig's base (73 mg) were added. The reaction was heated under reflux for one day. After cooling and dilution with dimethylsulfoxide (4 mL) the reaction was purified by preparative HPLC using a 250x50 mm C18 column and eluting with 20-100% CH<sub>3</sub>CN vs. 0.1% trifluoroacetic acid in water, giving the product as a trifluoroacetate salt. The trifluoroacetic acid salt was dissolved in dichloromethane (6 mL) and washed with 50% aqueous NaHCO<sub>3</sub>. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-

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$d_6$ )  $\delta$  11.72 (s, 1H), 8.43 (d, 1H), 8.22 (dd, 1H), 8.01 (d, 1H), 7.55 (m, 3H), 7.36 (m, 3H), 7.03 (d, 2H), 6.68 (dd, 1H), 6.41 (m, 1H), 6.17 (d, 1H), 5.83 (s, 2H), 4.40 (d, 2H), 3.78 (m, 2H), 3.59 (m, 2H), 3.08 (br m, 4H), 2.73 (br s, 2H), 2.18 (m, 8H), 1.96 (s, 2H), 1.84 (m, 4H), 1.39 (m, 4H), 0.92 (s, 6H), 0.75 (t, 3H).

## Example 369

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}<sup>(2)H<sub>8</sub></sup>piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 369A

methyl 4-[(2,2,3,3,5,5,6,6-<sup>2)H<sub>8</sub></sup>)piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoate

Into a 40 mL vial were added EXAMPLE 3H (1.55 g) and piperazine- $d_8$  (2.040 g) in dimethylsulfoxide (13 mL). The solution was heated to 85° C. for 2.5 hours, and was then allowed to cool to room temperature overnight. The mixture was transferred to a 120 mL flask and was cooled to 5-10° C. Dichloromethane (30 mL) was added, then water (10 mL) was added via syringe over 5 minutes maintaining temp at no more than 15° C. The layers were separated and the organic layer was washed with water (4×10-15 mL) until pH of aqueous layer was 8-9. The organic layer was filtered through Na<sub>2</sub>SO<sub>4</sub> and rinsed with dichloromethane (5 mL), and concentrated to provide the title compound.

## Example 369B

methyl 4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}<sup>(2)H<sub>8</sub></sup>piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoate

In a 100 mL round-bottomed flask, EXAMPLE 369A (3.4 g), EXAMPLE 290B (1.321 g) and dichloromethane (3 mL) were added to a 100 mL round bottom flask at room temperature. To a separate 50 mL 3 neck round bottom flask, sodium triacetoxymethylborohydride (1.330 g) and dichloromethane (12 mL) were added to give a slurry. After cooling the 50 mL round bottom flask to 18-20° C., the piperazine adduct/aldehyde solution was added via syringe over 5 minutes. The triacetoxymethylborohydride gradually dissolved to give a clear solution after 5 minutes. After an additional 10 minutes, the solution became hazy. After 16 hours, the reaction was cooled to 5-10° C. Saturated aqueous NaHCO<sub>3</sub> (12 mL) was added over 5 minutes maintaining the temperature at no more than 10° C. The layers were separated and the organic layer was washed with saturated aqueous NaHCO<sub>3</sub>, and 10% NaCl (12 mL), and then filtered through Na<sub>2</sub>SO<sub>4</sub> and rinsed with dichloromethane (4 mL). The solution was concentrated on a rotovap, and chase concentrated with methanol (40 mL). The resulting solution was cooled to 5-10° C., and the product precipitated. The solution was mixed at room temperature for 30 minutes, then filtered and rinsed with methanol (5 mL), and the product was air dried.

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## Example 369C

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}<sup>(2)H<sub>8</sub></sup>piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoic acid

The title compound was prepared by substituting EXAMPLE 369B for EXAMPLE 15G in EXAMPLE 15H.

## Example 369D

4-[4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}<sup>(2)H<sub>8</sub></sup>piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

To a mixture of EXAMPLE 369C (2.0 g), EXAMPLE 1F (1.1 g) and N,N-dimethylpyridin-4-amine (0.7 g) in dichloromethane (20 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (0.8 g). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with N,N-dimethylethane-1,2-diamine (0.6 g) and stirred at room temperature for 3 hours. The mixture was extracted with 20% aqueous acetic acid and washed with 5% aqueous NaCl. Methanol (2 mL) and ethyl acetate (18 mL) were added and the precipitate was collected by filtration to provide the title compound. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.71 (s, 1H), 11.37 (s, br, 1H), 8.60 (t, 1H), 8.55 (d, 1H), 8.04 (d, 1H), 7.80 (dd, 1H), 7.47-7.54 (m, 3H), 7.31-7.34 (m, 2H), 7.09 (d, 1H), 7.01-7.03 (m, 2H), 6.67 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.83 (dd, 2H), 3.21-3.30 (m, 4H), 3.00-3.10 (s, 4H), 2.75 (s, 2H), 2.05-2.24 (m, 6H), 1.95 (s, 2H), 1.80-1.93 (m, 1H), 1.55-1.64 (m, 2H), 1.37 (t, 2H), 1.18-1.31 (m, 2H), 0.90 (s, 6H).

## Example 370

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({3-[(tetrahydro-2H-pyran-4-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-yl]sulfonyl}benzamide

## Example 370A

5-amino-6-((tetrahydro-2H-pyran-4-yl)methylamino)pyridine-3-sulfonamide

A mixture of EXAMPLE 364E (0.16 g) and 5% palladium on carbon (0.025 g) in ethanol (5 mL) was treated with a balloon of hydrogen. The reaction mixture was stirred overnight. The solid was filtered off. The filtrate was concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

## Example 370B

3-((tetrahydro-2H-pyran-4-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridine-6-sulfonamide

EXAMPLE 370A (0.085 g) in water (10 mL) was treated with concentrated H<sub>2</sub>SO<sub>4</sub> (0.5 mL). The solution was cooled

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to 0° C. To this solution was added NaNO<sub>2</sub> (0.023 g) in water (1 mL) dropwise. The solution was stirred for 1 hour at 0° C. The reaction mixture was poured into saturated NaHCO<sub>3</sub> solution, and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound.

## Example 370C

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(3-((tetrahydro-2H-pyran-4-yl)methyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylsulfonyl)benzamide

This example was prepared by substituting EXAMPLE 370B for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.60 (s, 1H), 9.11 (s, 1H), 8.92 (d, 1H), 7.96 (d, 1H), 7.55 (d, 1H), 7.45-7.46 (m, 1H), 7.42 (s, 1H), 7.36 (d, 2H), 7.05 (d, 2H), 6.66 (dd, 1H), 6.32 (s, 1H), 6.22 (s, 1H), 4.63 (d, 2H), 3.80 (dd, 2H), 3.21-3.30 (m, 2H), 3.16 (s, 4H), 2.83 (s, 2H), 2.19-2.29 (m, 6H), 1.97 (s, 2H), 1.33-1.41 (m, 6H), 0.93 (s, 2H).

## Example 371

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(6-((trans-4-hydroxy-4-methylcyclohexyl)methyl)amino)-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 371A

6-((trans-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 364D for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 376B for EXAMPLE 138C in EXAMPLE 138D. The title compound was isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5μ, C18(2), 250×21.20 mm, 5 Å) eluting with 20-80% acetonitrile in water with 0.1% TFA.

## Example 371B

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(6-((trans-4-hydroxy-4-methylcyclohexyl)methyl)amino)-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 371A for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.63 (s, 1H), 11.53-10.99 (m, 1H), 8.91 (s, 1H), 8.71 (dd, 2H), 8.01 (d, 1H), 7.61-7.44 (m, 3H), 7.44-7.28 (m, 2H), 7.12-6.97 (m, 2H), 6.76-6.61 (m, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 3.92 (s, 1H), 3.48 (t, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.24 (dd, 6H), 1.96 (s, 2H), 1.37 (ddd, 11H), 1.07 (s, 3H), 0.93 (s, 6H).

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## Example 372

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(5-cyano-6-([4-fluoro-1-(oxetan-3-yl)piperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 372A

ethyl  
4-fluoro-1-(oxetan-3-yl)piperidine-4-carboxylate

To 1-tert-butyl 4-ethyl 4-fluoropiperidine-1,4-dicarboxylate (1.00 g) was added HCl (4.0M in dioxane, 4.54 mL). After 1 hour the reaction was concentrated and dried under high vacuum. The resulting solid was dissolved in dichloromethane (5 mL) and treated with sodium triacetoxyborohydride (1.155 g) and oxetan-3-one (0.262 g) and stirred overnight. The reaction was quenched with saturated NaHCO<sub>3</sub> solution (20 mL) and extracted into dichloromethane (2×25 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting with a gradient of 0.5% to 3.75% methanol/dichloromethane over 40 minutes (flow=30 mL/minute) gave the title compound.

## Example 372B

(4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methanol

To a solution of EXAMPLE 372A (0.59 g) in tetrahydrofuran (5 mL) was added lithium aluminum hydride (1.80 mL) at 0° C. The reaction was removed from the ice bath and allowed to warm to room temperature. The reaction was quenched by the dropwise addition of 0.6 mL of water followed by 0.2 mL of 2N aqueous NaOH. The reaction was filtered through diatomaceous earth and rinsed with ethyl acetate (50 mL). The organics were concentrated and loaded onto silica gel (Reveleris 40 g) and eluted using a gradient of 0.75% to 7.5% methanol/dichloromethane over 30 minute (flow=40 mL/minutes) to give the title compound.

## Example 372C

5-bromo-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 372B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 36A for 4-fluoro-3-nitrobenzenesulfonamide in EXAMPLE 24A.

## Example 372D

5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 372C for EXAMPLE 36B in EXAMPLE 36C.

## Example 372E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(5-cyano-6-((4-fluoro-1-(oxetan-3-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 372D for EXAMPLE 11B in EXAMPLE 11D.

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<sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.58 (s, 1H), 8.71 (s, 1H), 8.52 (s, 1H), 7.96 (d, 1H), 7.57 (d, 1H), 7.48-7.30 (m, 4H), 7.06 (d, 2H), 6.68 (d, 1H), 6.37-6.22 (m, 2H), 4.65-4.40 (m, 6H), 3.58 (s, 1H), 3.12 (s, 6H), 2.84-2.59 (m, 4H), 2.17 (s, 6H), 1.96 (d, 6H), 1.41 (s, 2H), 0.93 (s, 6H).

## Example 373

N-(4-{[4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzoyl]sulfamoyl}-2-nitrophenyl)morpholine-4-carboxamide

## Example 373A

morpholine-4-carboxamide

A solution of morpholine-4-carbonyl chloride (2.0 g) in methanol (10 mL) and 7 N NH<sub>3</sub> in methanol (5 mL) was stirred at 45° C. overnight. The mixture was concentrated to give a solid, which was dried under vacuum.

## Example 373B

N-(2-nitro-4-sulfamoylphenyl)morpholine-4-carboxamide

This example was prepared by substituting EXAMPLE 373A for (tetrahydro-2H-pyran-4-yl)methanol in EXAMPLE 24A.

## Example 373C

N-(4-(N-(2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)sulfamoyl)-2-nitrophenyl)morpholine-4-carboxamide

This example was prepared by substituting EXAMPLE 373B for EXAMPLE 130C in EXAMPLE 130D. <sup>1</sup>H NMR (500 MHz, pyridine-d<sub>5</sub>) δ 13.02 (s, 1H), 10.41 (s, 1H), 9.27 (d, 1H), 8.81 (d, 1H), 8.50 (dd, 1H), 8.40 (d, 1H), 8.09 (d, 1H), 7.65 (m, 2H), 7.44 (d, 2H), 7.07 (d, 2H), 6.76 (dd, 1H), 6.54 (d, 1H), 6.48 (m, 1H), 3.67 (m, 4H), 3.58 (m, 4H), 3.07 (m, 4H), 2.77 (s, 2H), 2.26 (t, 2H), 2.14 (m, 4H), 1.97 (s, 2H), 1.39 (t, 2H), 0.94 (s, 6H).

## Example 374

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-{[4-(methoxymethyl)cyclohexyl]methyl}amino]-3-nitrophenyl}sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 374A

(4,4-diethoxycyclohexyl)methanol

Ethyl 4,4-diethoxycyclohexanecarboxylate (6.67 g) synthesized according to a literature procedure (*European Journal of Organic Chemistry*, 2008, 5, 895) in tetrahydrofuran (60 mL) was treated with 2 M lithium aluminum hydride in tetrahydrofuran (14.5 mL) at 0° C. for 1 hour. Water (3 mL) was slowly added to quench the reaction. The precipitates

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were filtered off and washed with ethyl acetate. The filtrate was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

## Example 374B

1,1-diethoxy-4-(methoxymethyl)cyclohexane

EXAMPLE 374A (665 mg) in tetrahydrofuran (20 mL) was treated with NaH (394 mg) for 30 minutes and then CH<sub>3</sub>I (0.267 mL) was slowly added. The resulting mixture was stirred overnight and the reaction was quenched with a few drops of water. The mixture was concentrated and the residue was suspended in water and extracted with dichloromethane. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography, and was eluted with 0-15% ethyl acetate in dichloromethane to provide the title compound.

## Example 374C

4-(methoxymethyl)cyclohexanone

EXAMPLE 374B (2.2 g) in a mixture of water (3 mL) and acetic acid (12 mL) was heated at 65° C. for 2 hours. The reaction mixture was concentrated. The residue was mixed with water and saturated aqueous NaHCO<sub>3</sub> and extracted with dichloromethane. The dichloromethane layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to provide the title compound.

## Example 374D

4-(methoxymethyl)cyclohexanecarbonitrile

To a cold (-10° C.) solution of EXAMPLE 374C (1.18 g) and toluenesulfonylmethyl isocyanide (2.268 g) in dimethoxyethane (3 mL) and absolute ethanol (0.1 mL) was added (in small portions) potassium tert-butoxide (2.235 g). The reaction mixture was continued to stir at <5° C. for 30 minutes, warmed to room temperature, heated at 35° C. for 30 minutes and then at room temperature for 2 hours. The reaction mixture was concentrated and the residue was dissolved in water-brine, and extracted with dichloromethane. The dichloromethane layer was purified by flash chromatography, and was eluted with 5% ethyl acetate in dichloromethane to provide the title compound.

## Example 374E

(4-(methoxymethyl)cyclohexyl)methanamine

To a solution of EXAMPLE 374D (460 mg) in tetrahydrofuran (15 mL) was added 2M lithium aluminum hydride in tetrahydrofuran (2.252 mL) slowly. The reaction mixture was stirred at room temperature for 1 hour, refluxed for 1 hour and cooled. 2 mL of 2M aqueous NaOH and water (5 mL) was added. The solid was filtered off and washed with ether. The filtrate was concentrated. The residue was mixed with dichloromethane (50 mL) and the resulting mixture was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to provide the title compound.

## Example 374F

4-((4-(methoxymethyl)cyclohexyl)methylamino)-3-nitrobenzenesulfonamide

EXAMPLE 374E (450 mg) and 4-fluoro-3-nitrobenzenesulfonamide (693 mg) in tetrahydrofuran (10 mL) were



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stirred overnight. The reaction mixture was concentrated and the residue was suspended in a mixture of CH<sub>3</sub>CN, methanol and water. The precipitates were collected, washed with water and dried to give the title compound.

## Example 374G

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-(4-((4-(methoxymethyl)cyclohexyl)methylamino)-3-nitrophenylsulfonyl)benzamide

The title compound was prepared as described in EXAMPLE 11D using EXAMPLE 374F in place of EXAMPLE 11B. <sup>1</sup>H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.69 (s, 1H), 11.40 (s, 1H), 8.53-8.61 (m, 2H), 8.04 (d, 1H), 7.77-7.82 (m, 1H), 7.47-7.55 (m, 3H), 7.34 (d, 2H), 7.02-7.09 (m, 3H), 6.68 (dd, 1H), 6.39 (dd, 1H), 6.19 (d, 1H), 3.18-3.27 (m, 5H), 3.04-3.14 (m, 5H), 2.75 (s, 2H), 2.11-2.24 (m, 6H), 1.95 (s, 2H), 1.69-1.84 (m, 3H), 1.33-1.63 (m, 7H), 0.84-1.05 (m, 9H).

## Example 375

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(5-chloro-6-([1-(1,3-thiazol-2-yl)piperidin-4-yl]methoxy)pyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 375A

methyl 1-(thiazol-2-yl)piperidine-4-carboxylate

A mixture of methyl piperidine-4-carboxylate (2.045 g), 2-bromothiazole (1.64 g), and Cs<sub>2</sub>CO<sub>3</sub> (5.86 g) in dimethylformamide (15 mL) was heated at 100° C. overnight. After it cooled to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the title compound.

## Example 375B

(1-(thiazol-2-yl)piperidin-4-yl)methanol

This example was prepared by substituting EXAMPLE 375A for EXAMPLE 339A in EXAMPLE 339B.

## Example 375C

5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 375B for (tetrahydro-2H-pyran-4-yl)methanol and EXAMPLE 40A for EXAMPLE 36A in EXAMPLE 36B.

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## Example 375D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-(5-chloro-6-((1-(thiazol-2-yl)piperidin-4-yl)methoxy)pyridin-3-ylsulfonyl)-4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzamide

This example was prepared by substituting EXAMPLE 375C for EXAMPLE 11B in EXAMPLE 11D. <sup>1</sup>H NMR (500 MHz, dimethylsulfoxide-d<sub>6</sub>) δ 11.65 (s, 1H), 8.49 (s, 1H), 8.17 (s, 1H), 8.01 (d, 1H), 7.54 (d, 1H), 7.48-7.49 (m, 2H), 7.35 (d, 2H), 7.14 (d, 1H), 7.05 (d, 2H), 6.80 (d, 1H), 6.67 (dd, 1H), 6.38 (dd, 1H), 6.21 (d, 1H), 4.28 (d, 2H), 3.92 (d, 2H), 2.98-3.10 (m, 6H), 2.86 (s, 2H), 2.30 (m, 4H), 2.03-2.15 (m, 3H), 1.96 (s, 2H), 1.96 (s, 2H), 1.82-1.86 (m, 2H), 1.33-1.44 (m, 4H), 0.93 (s, 6H).

## Example 376

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-[(6-([[(cis-4-hydroxy-4-methylcyclohexyl)methyl]amino]-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 376A

tert-butyl(4-hydroxy-4-methylcyclohexyl)methylcarbamate

A solution of tert-butyl(4-oxocyclohexyl)methylcarbamate (1.00 g) was dissolved in tetrahydrofuran (20 mL) and cooled to -78° C. Methylmagnesium bromide (4.40 mL) was added dropwise. The reaction was stirred for 2 hours at -78° C. then allowed to warm to 0° C. and stirred for 30 minutes. The resulting suspension was quenched with water (10 mL), diluted with ether (50 mL), washed with ammonium chloride (25 mL), washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Reveleris 80 g) eluting using a gradient of 5% to 50% ethyl acetate/dichloromethane over 30 minutes (flow=60 mL/min) gave the title compound as a 2:1 mixture of cis and trans isomers.

## Example 376B

4-(aminomethyl)-1-methylcyclohexanol

To a solution of EXAMPLE 376A (0.75 g) in dichloromethane (3 mL) was added a few drops of water followed by trifluoroacetic acid (1.19 mL) and the reaction stirred at room temperature. After stirring for 2 h added additional trifluoroacetic acid (0.5 mL). After an additional 4 h the reaction was concentrated and dried under high vacuum. The resulting oily solid was triturated with diethyl ether with sonication. Filtration and washing with diethyl ether gave the title compound as a trifluoroacetic acid salt and a mixture of cis and trans isomers.

## Example 376C

6-((cis-4-hydroxy-4-methylcyclohexyl)methylamino)-5-nitropyridine-3-sulfonamide

This example was prepared by substituting EXAMPLE 376D for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 376B for (4-fluorotetrahydro-2H-pyran-4-yl)

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methanamine in EXAMPLE 138D. The title compound was isolated by reverse phase Gilson Prep HPLC system with a Phenomenex prep column (Luna, 5 $\mu$ , C18(2), 250 $\times$ 21.20 mm, 5  $\text{\AA}$ ) eluting with 20-80% acetonitrile in water with 0.1% TFA.

## Example 376D

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([(6-([2-(4-chlorophenyl)-4-methylcyclohexyl)methyl]amino)-5-nitropyridin-3-yl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

This example was prepared by substituting EXAMPLE 376C for EXAMPLE 11B in EXAMPLE 11D.  $^1\text{H}$  NMR (500 MHz, dimethylsulfoxide- $d_6$ )  $\delta$  11.64 (s, 1H), 8.91 (s, 1H), 8.72 (d, 1H), 8.70 (d, 1H), 8.01 (d, 1H), 7.47-7.54 (m, 3H), 7.35 (d, 2H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.36 (dd, 1H), 6.21 (d, 1H), 3.93 (s, 1H), 3.48 (t, 2H), 3.10 (s, 4H), 2.83 (s, 2H), 2.15-2.33 (m, 6H), 1.96 (s, 1H), 1.34-1.59 (m, 9H), 1.17-1.24 (m, 2H), 1.07 (s, 2H), 0.92 (s, 6H).

## Example 377

4-(4-([2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([(4-([(trans-4-hydroxy-4-methylcyclohexyl)methyl]-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

The title compound was prepared by substituting EXAMPLE 378D for EXAMPLE 1E and EXAMPLE 337M for EXAMPLE 1F in EXAMPLE 1G.  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.07 (s, 1H), 9.31 (d, 1H), 8.68 (t, 1H), 8.44 (d, 1H), 8.37 (dd, 1H), 8.10 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 6.92 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 3.20 (m, 5H), 3.06 (t, 4H), 2.77 (m, 2H), 2.57 (d, 1H), 2.49 (m, 1H), 2.17 (m, 6H), 1.86 (m, 5H), 1.69 (m, 4H), 1.40 (s, 3H), 1.23 (m, 5H).

## Example 378

4-(4-([2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

## Example 378A

2-chloro-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

Dimethylformamide (1.298 mL) in dichloromethane (2.0 mL) at  $-10^\circ\text{C}$ . was treated dropwise with  $\text{POCl}_3$  (1.426 mL) to give a colorless solution. The mixture was stirred 5 minutes and then warmed to room temperature and stirred 30 minutes. The solution was cooled to  $-10^\circ\text{C}$ ., treated dropwise with a solution of 4-methoxy-4-methylcyclohexanone (1.74 g) in dichloromethane (2.5 mL), and stirred for 4 hours at ambient temperature. The reaction mixture was poured over a mixture

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of ice and 25% aqueous sodium acetate solution. After the ice melted, the reaction mixture was poured into a separatory funnel and extracted with diethyl ether (4 $\times$ 125 mL). The diethyl ether extracts were washed with  $\text{NaHCO}_3$  solution and brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated. The concentrate was chromatographed on silica gel with 0 to 5% ethyl acetate in hexanes as the eluent.

## Example 378B

2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enecarbaldehyde

EXAMPLE 378A (1.55 g), 4-chlorophenylboronic acid (1.542 g),  $\text{PdOAc}_2$  (0.055 g),  $\text{K}_2\text{CO}_3$  (2.84 g) and tetrabutylammonium bromide (2.65 g) were combined in a 50-mL round-bottomed flask equipped with a magnetic stir bar. Water (9.13 mL) was added. The vial was flushed with nitrogen, capped and stirred at  $45^\circ\text{C}$ . for 14 hours. The reaction mixture was cooled to room temperature and partitioned between brine and diethyl ether. The organic layer was washed with brine, dried ( $\text{MgSO}_4$ ), filtered through a plug of celite, concentrated and chromatographed on silica gel with 5 to 20% ethyl acetate in hexanes as the eluent.

## Example 378C

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

The title compound was prepared by substituting EXAMPLE 378B for 4'-chlorobiphenyl-2-carboxaldehyde and EXAMPLE 15F for tert-butyl piperazine-1-carboxylate in EXAMPLE 1A except that a small amount of DMSO was added to the reaction mixture.

## Example 378D

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

The title compound was prepared by substituting EXAMPLE 378C for EXAMPLE 15G in EXAMPLE 15H.

## Example 378E

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-(4-((2-(4-chlorophenyl)-5-methoxy-5-methylcyclohex-1-enyl)methyl)piperazin-1-yl)-N-(3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)phenyl)sulfonyl)benzamide

The title compound was prepared by substituting EXAMPLE 378D for EXAMPLE 1E in EXAMPLE 1G.  $^1\text{H}$  NMR (500 MHz, pyridine- $d_5$ )  $\delta$  13.07 (s, 1H), 9.31 (d, 1H), 8.68 (t, 1H), 8.43 (d, 1H), 8.37 (dd, 1H), 8.09 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.41 (m, 2H), 7.09 (m, 2H), 6.90 (d, 1H), 6.74 (dd, 1H), 6.52 (d, 1H), 6.50 (dd, 1H), 3.97 (dd, 2H), 3.30 (td, 2H), 3.21 (s, 3H), 3.15 (m, 2H), 3.06 (t, 4H), 2.77 (m, 2H), 2.57 (d, 1H), 2.50 (m, 1H), 2.16 (m, 6H), 1.81 (m, 2H), 1.63 (m, 1H), 1.57 (dd, 2H), 1.32 (m, 2H), 1.21 (s, 3H).

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What is claimed is:

1. A method of treating a cancer selected from the group consisting of chronic lymphocytic leukemia, lymphoblastic leukemia, follicular lymphoma, a lymphoid malignancy of T cell or B cell origin, myelogenous leukemia, myeloma and breast cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the cancer is chronic lymphocytic leukemia.

3. The method of claim 1, wherein the cancer is lymphoblastic leukemia.

4. A method of treating chronic lymphocytic leukemia in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

5. A method of treating lymphoblastic leukemia in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

6. A method of treating myeloma in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

7. A method of treating breast cancer in a patient, said method comprising administering to the patient a therapeutically effective amount of a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

\* \* \* \* \*

# EXHIBIT C



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(12) **United States Patent**  
**Catron et al.**(10) **Patent No.:** **US 8,722,657 B2**  
(45) **Date of Patent:** **May 13, 2014**(54) **SALTS AND CRYSTALLINE FORMS OF AN APOPTOSIS-INDUCING AGENT**(75) Inventors: **Nathaniel Catron**, Vernon Hills, IL (US); **Shuang Chen**, Gurnee, IL (US); **Yuchuan Gong**, Waukegan, IL (US); **Geoff G. Zhang**, Vernon Hills, IL (US)(73) Assignee: **Abbvie Inc.**, North Chicago, IL (US)

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(21) Appl. No.: **13/301,257**(22) Filed: **Nov. 21, 2011**(65) **Prior Publication Data**

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None

See application file for complete search history.

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Primary Examiner — Anna Pagonakis

(74) Attorney, Agent, or Firm — Jones Day

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**ABSTRACT**

Salts and crystalline forms of 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}-sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide are suitable active pharmaceutical ingredients for pharmaceutical compositions useful in treatment of a disease characterized by overexpression of one or more anti-apoptotic Bcl-2 family proteins, for example cancer.

**3 Claims, 14 Drawing Sheets**

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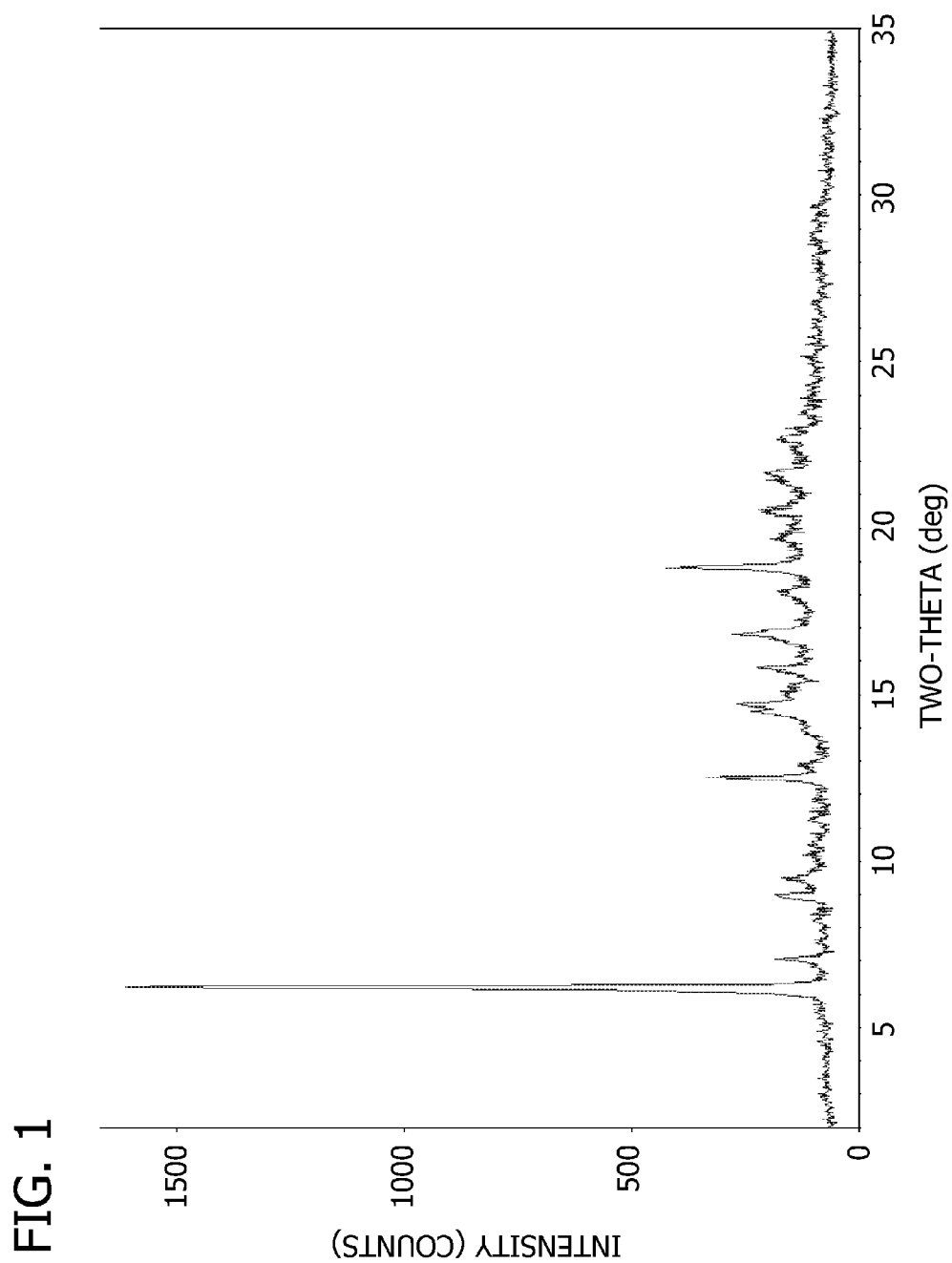
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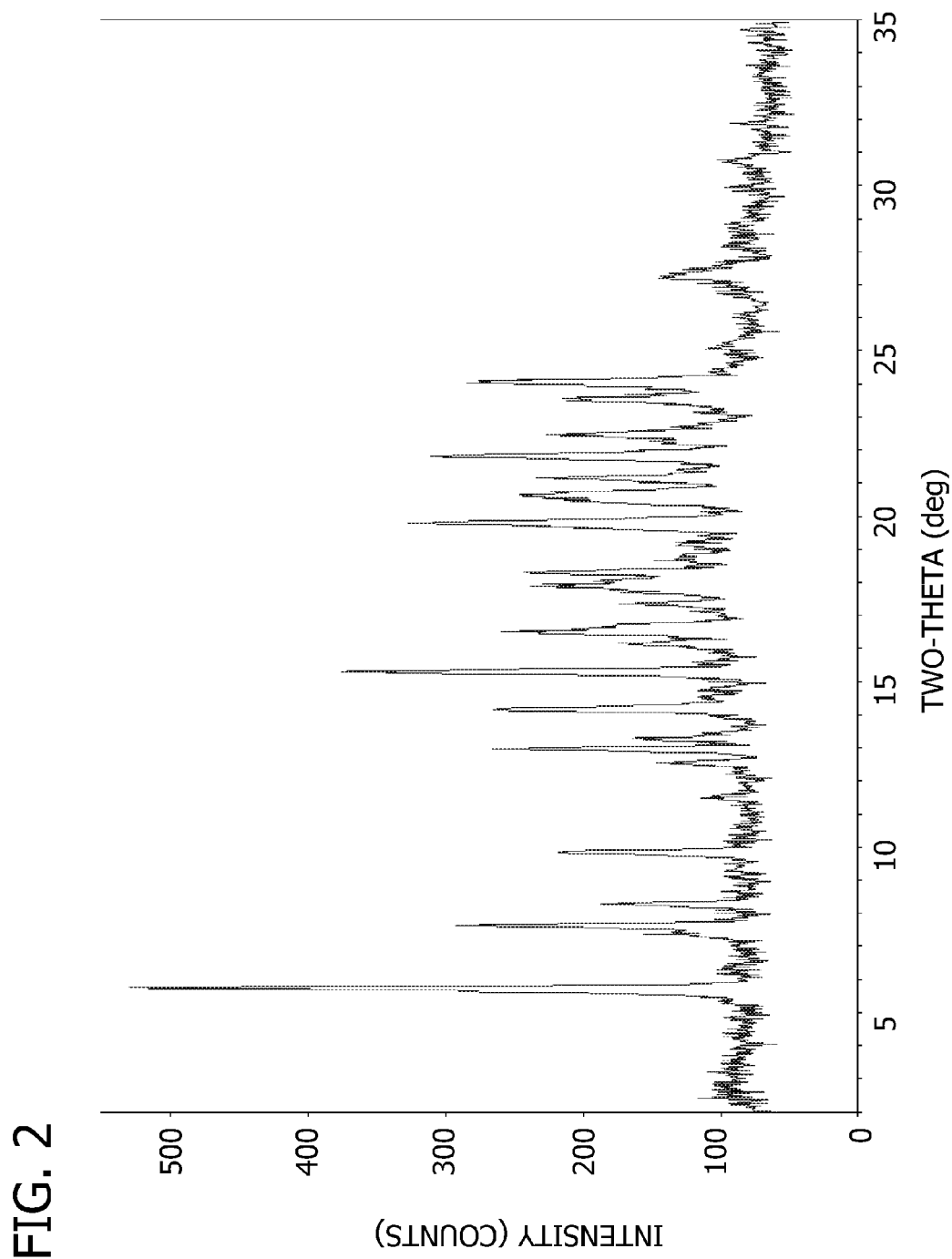


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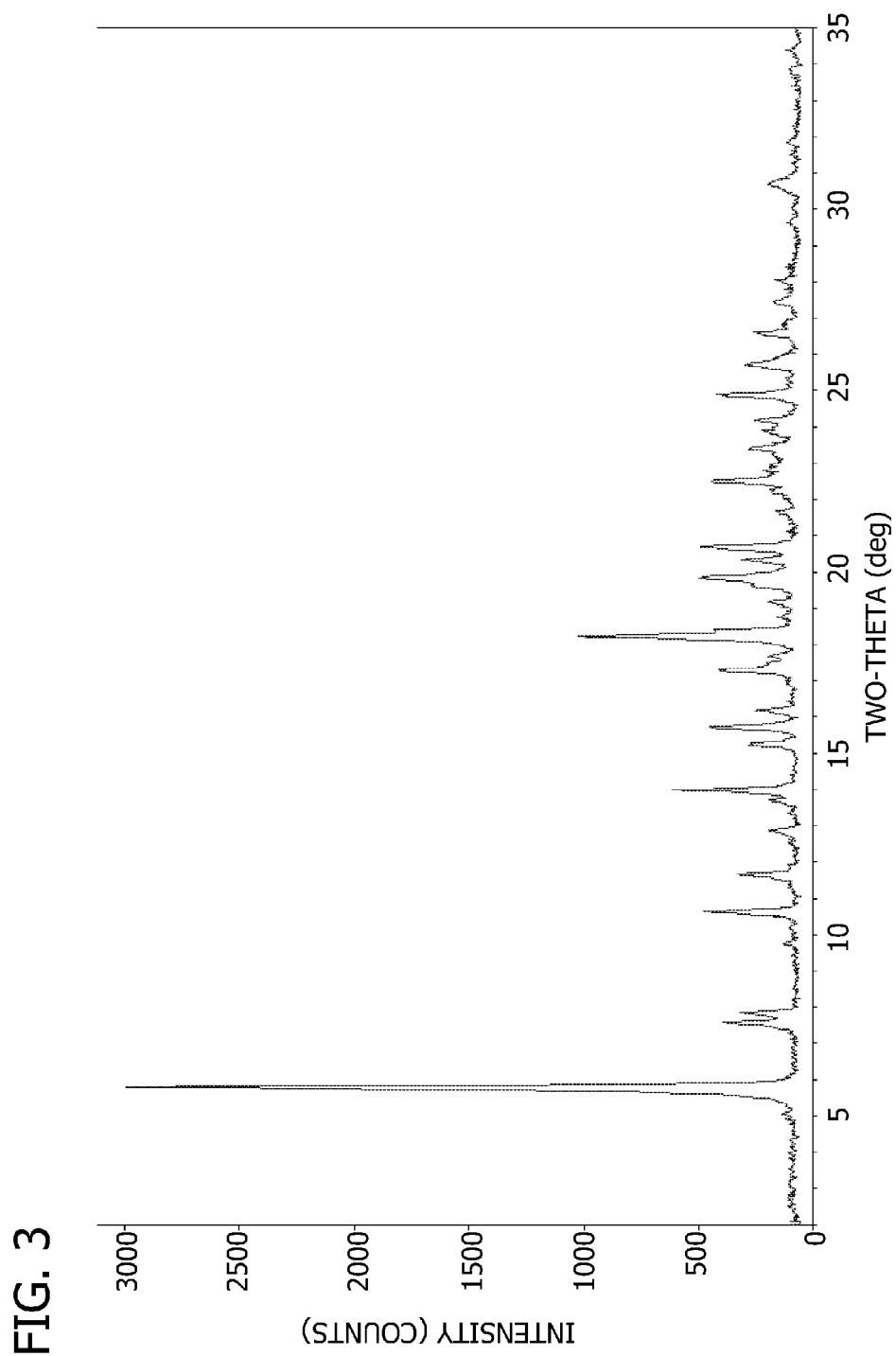


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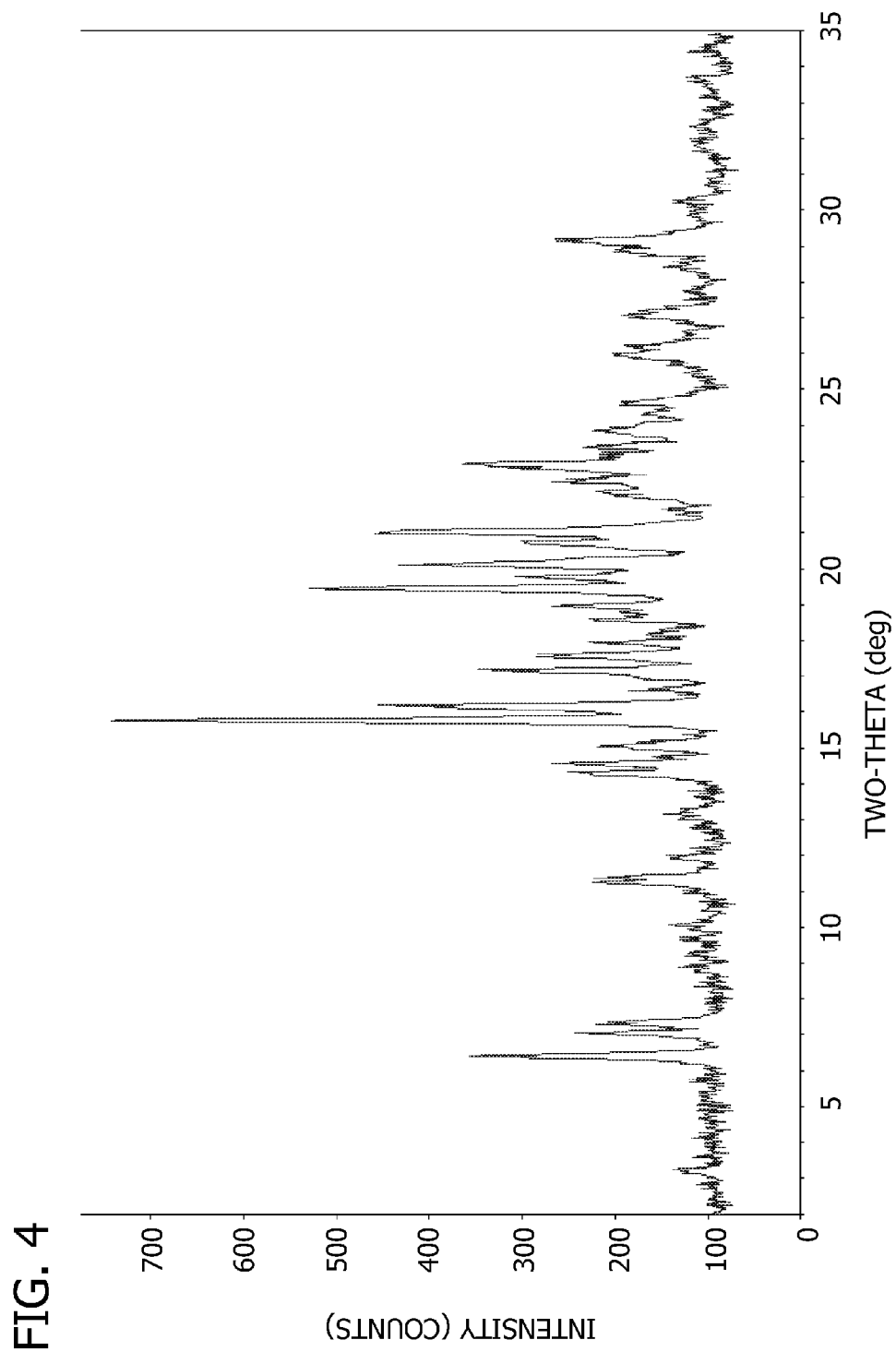


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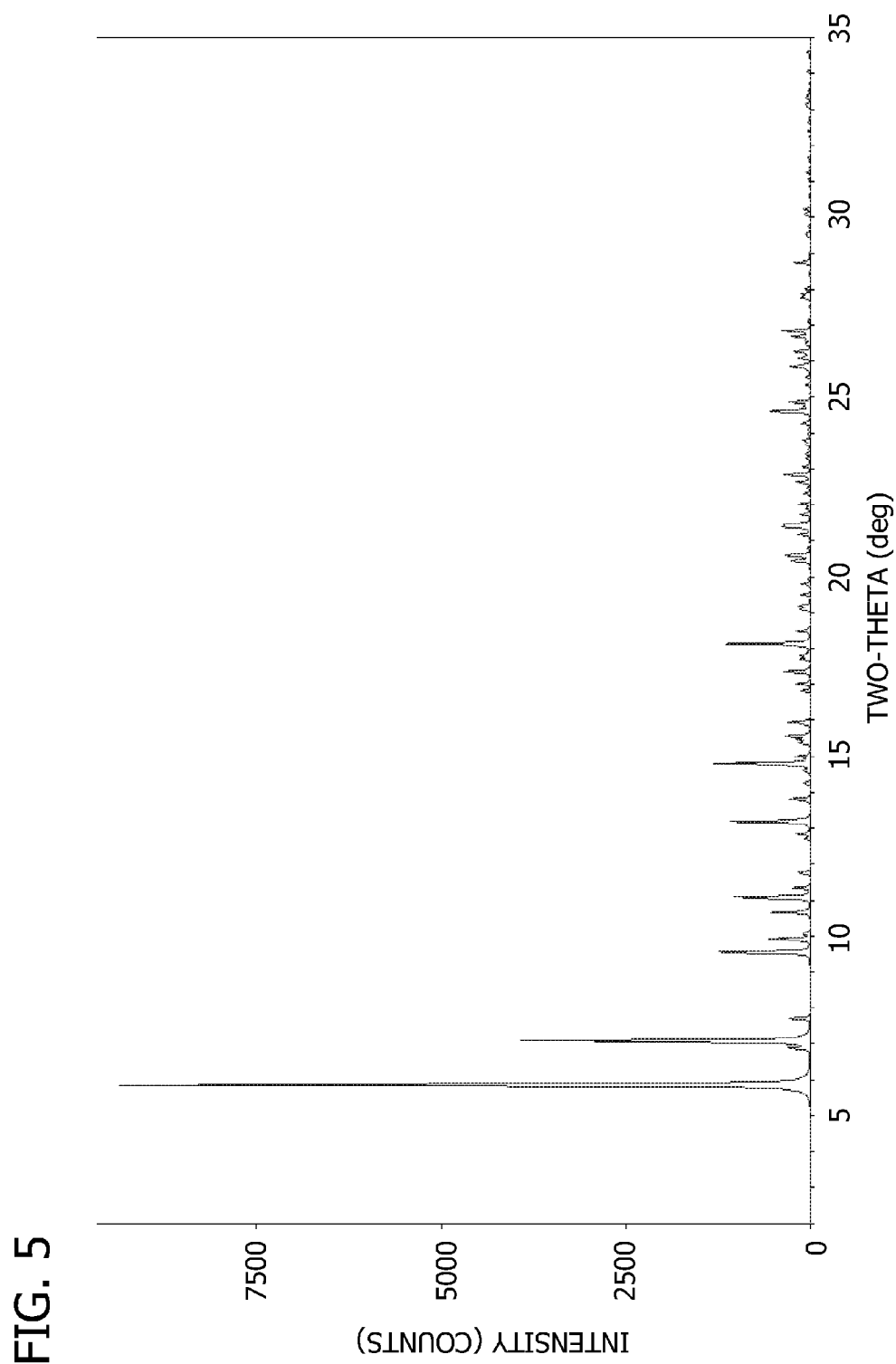


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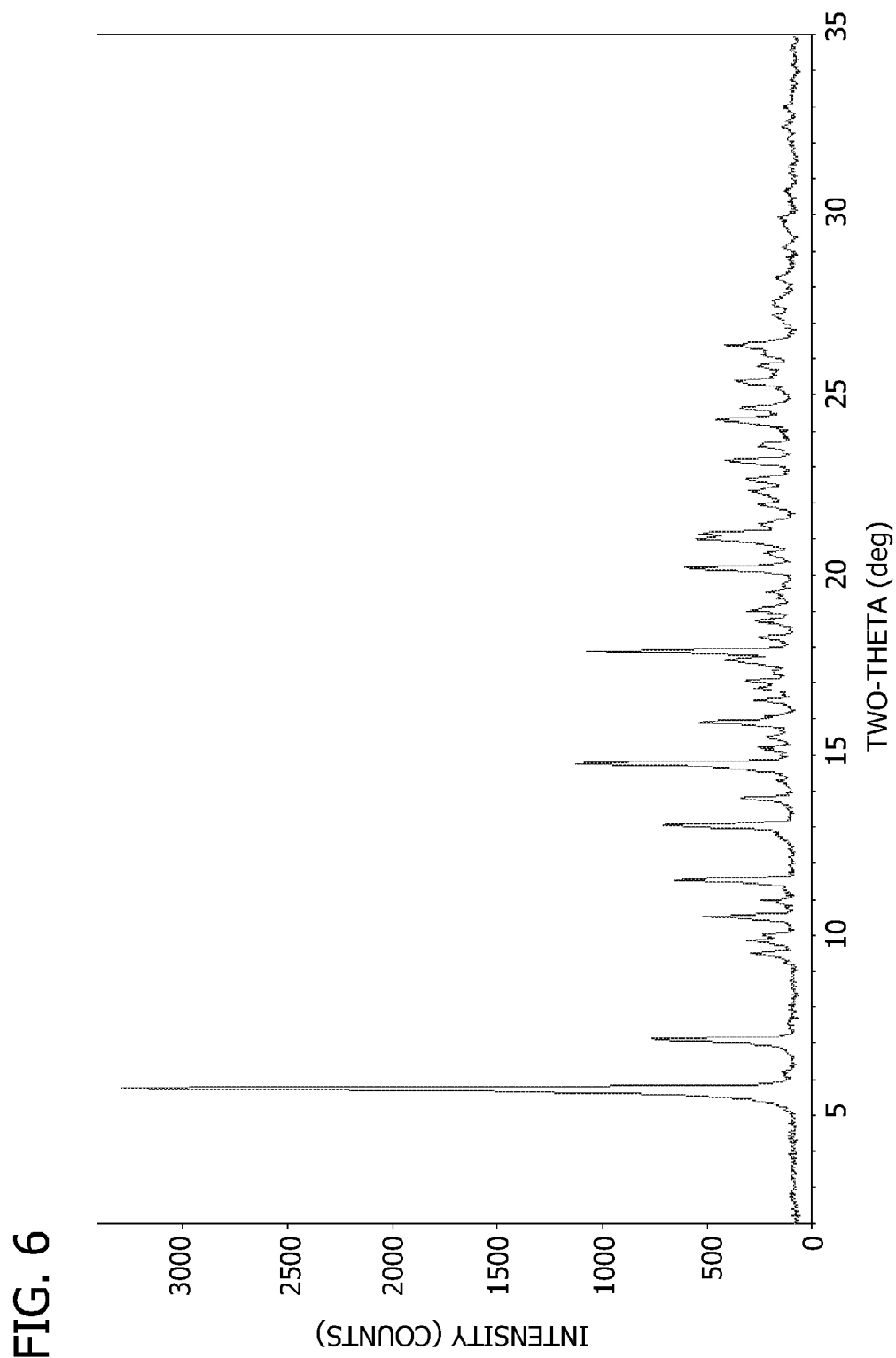


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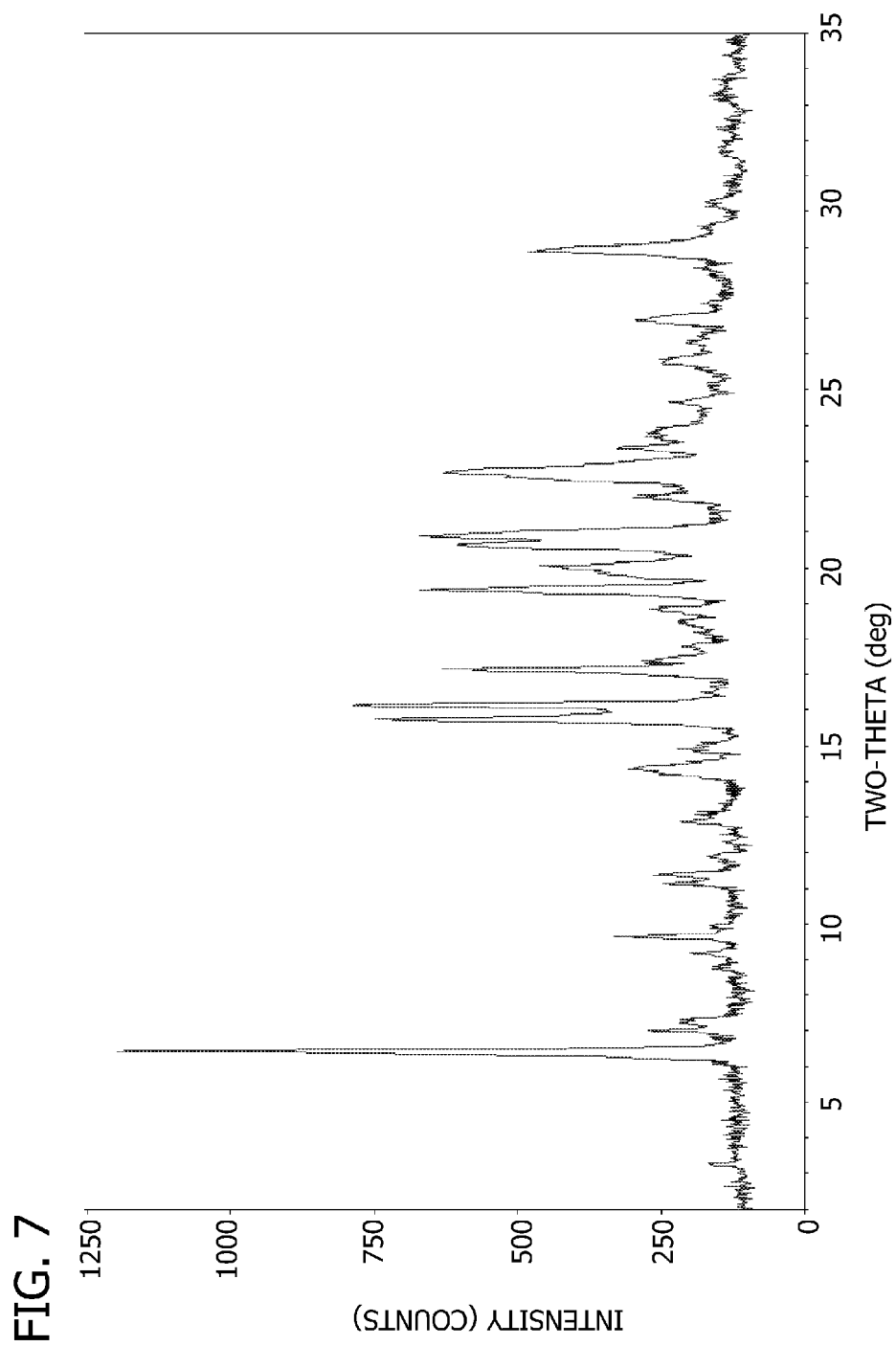


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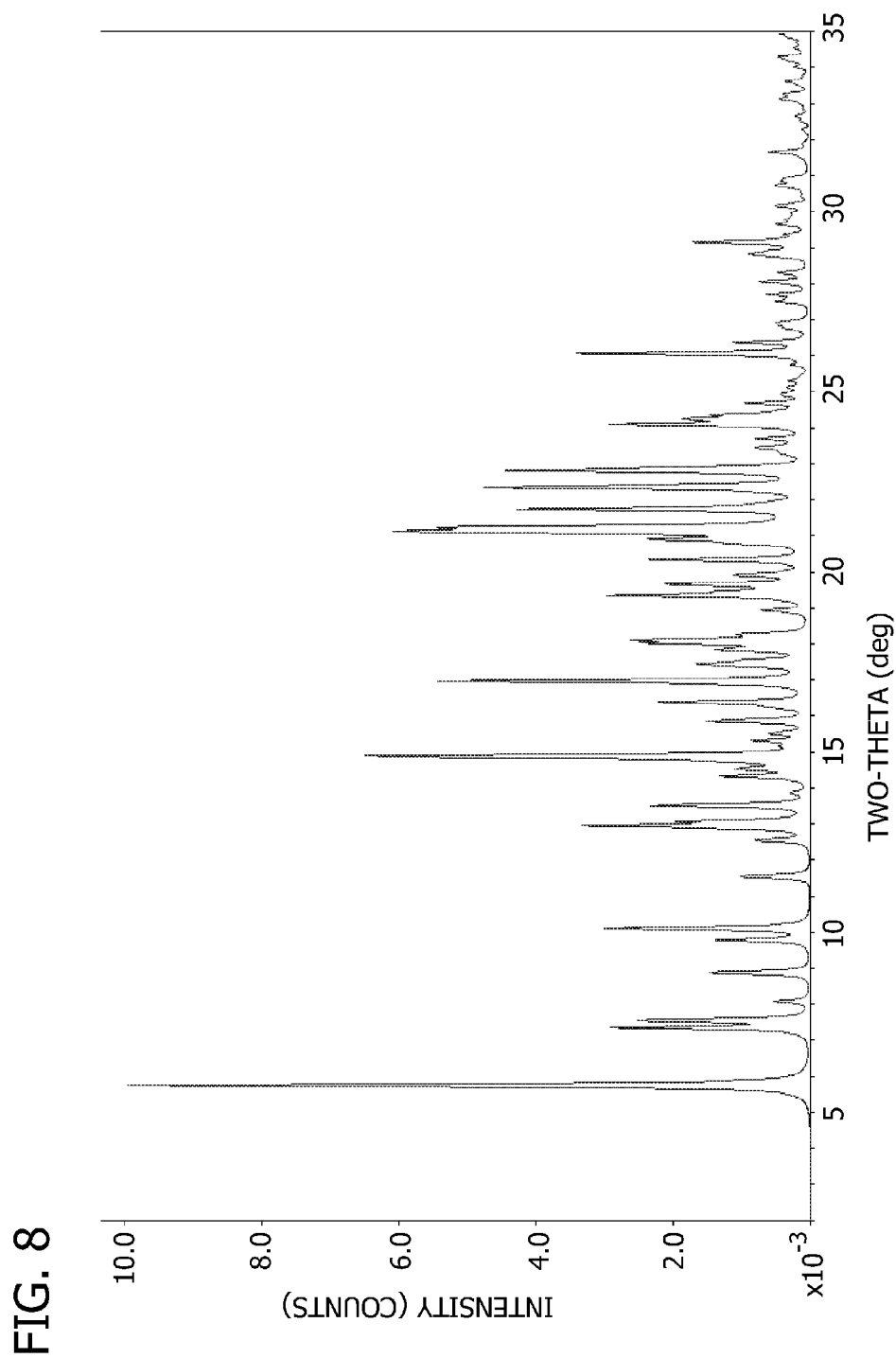


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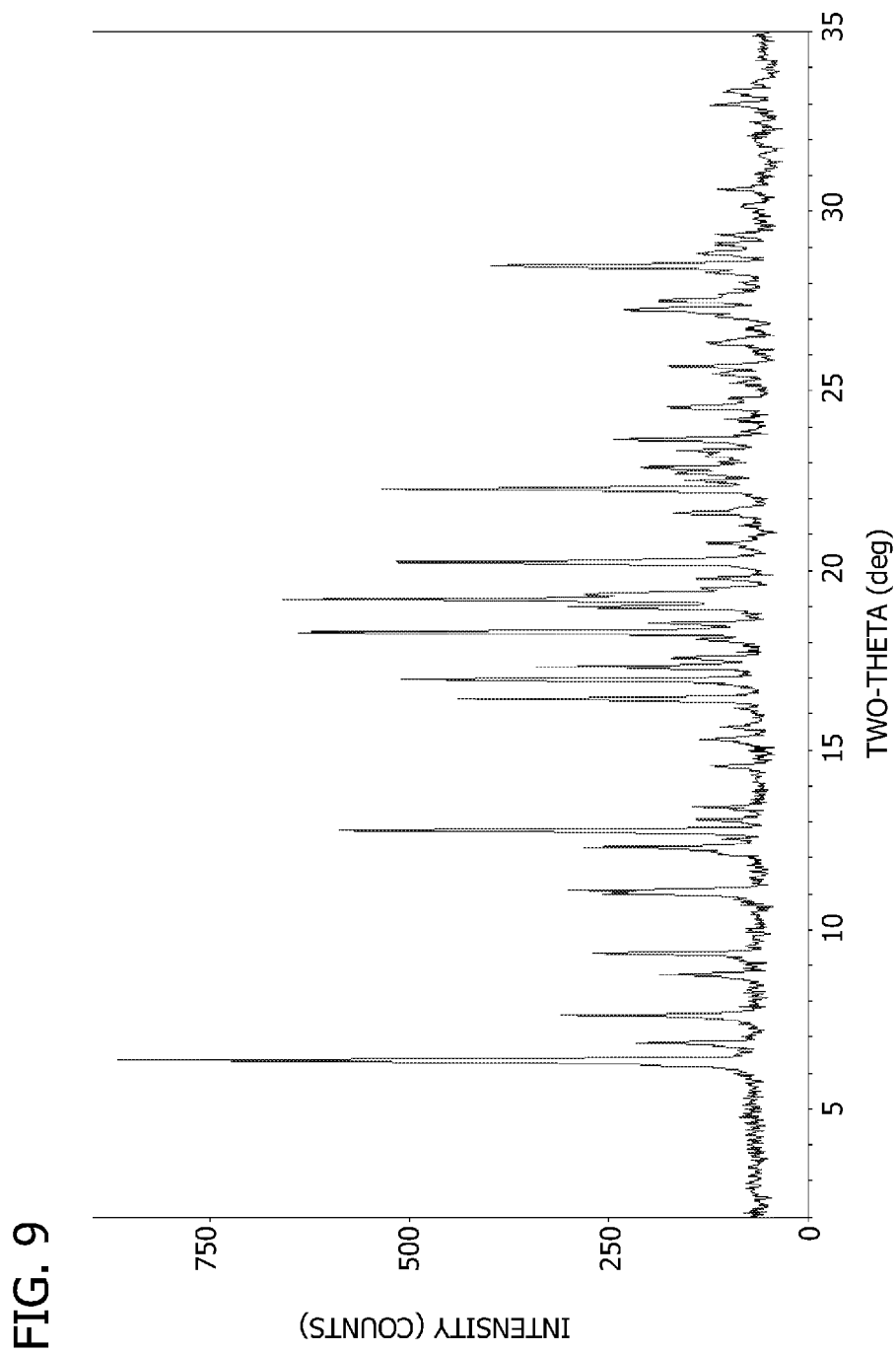


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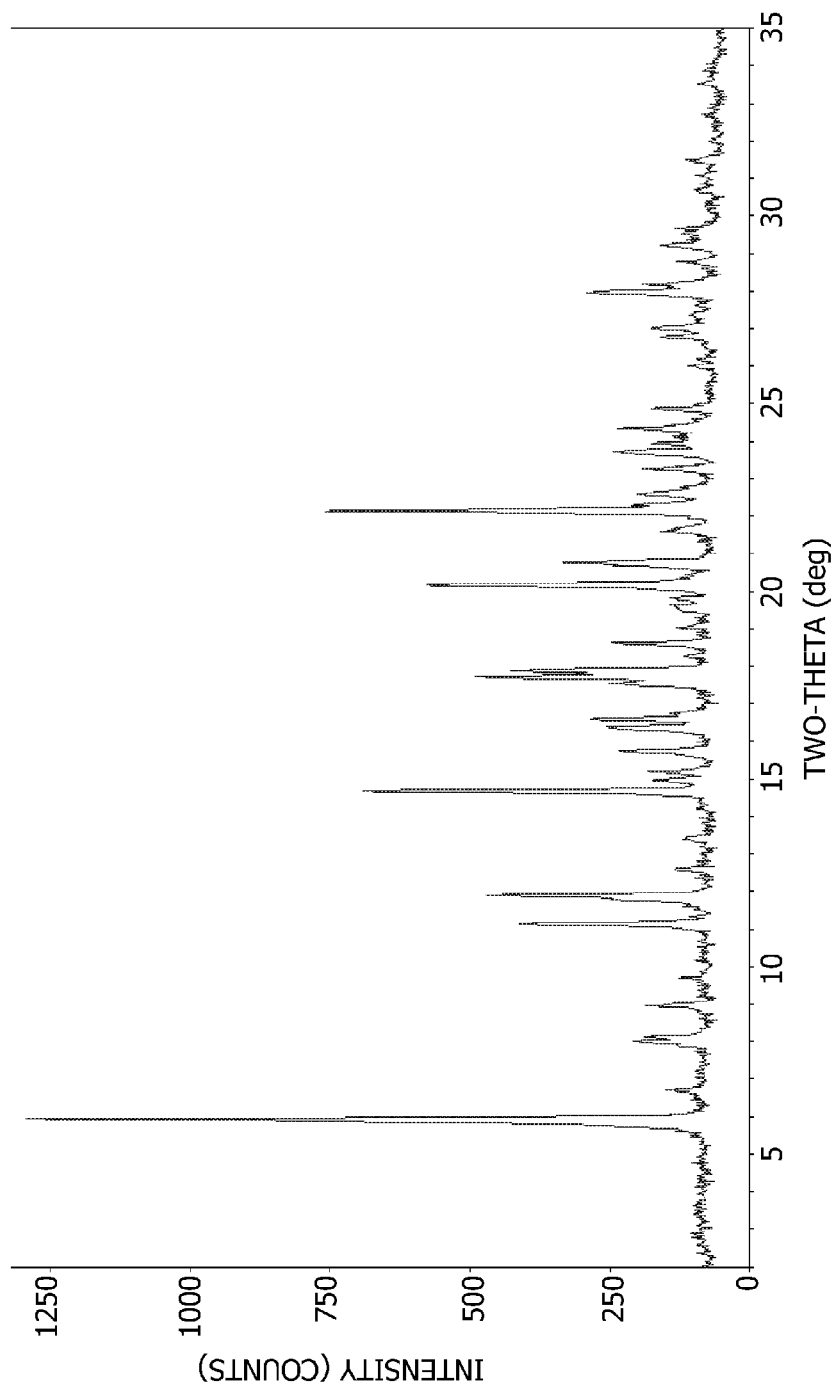
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**FIG. 10**

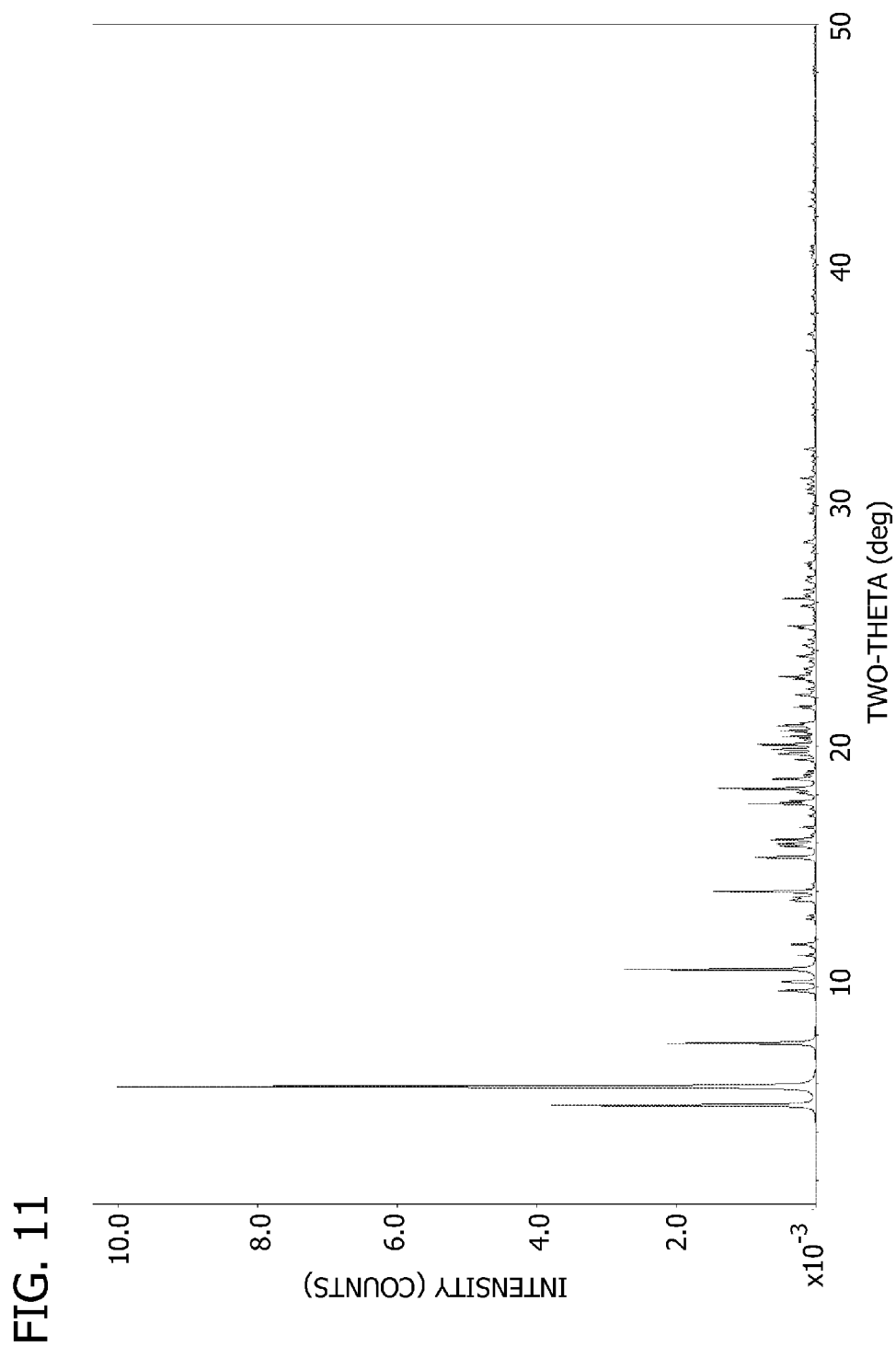


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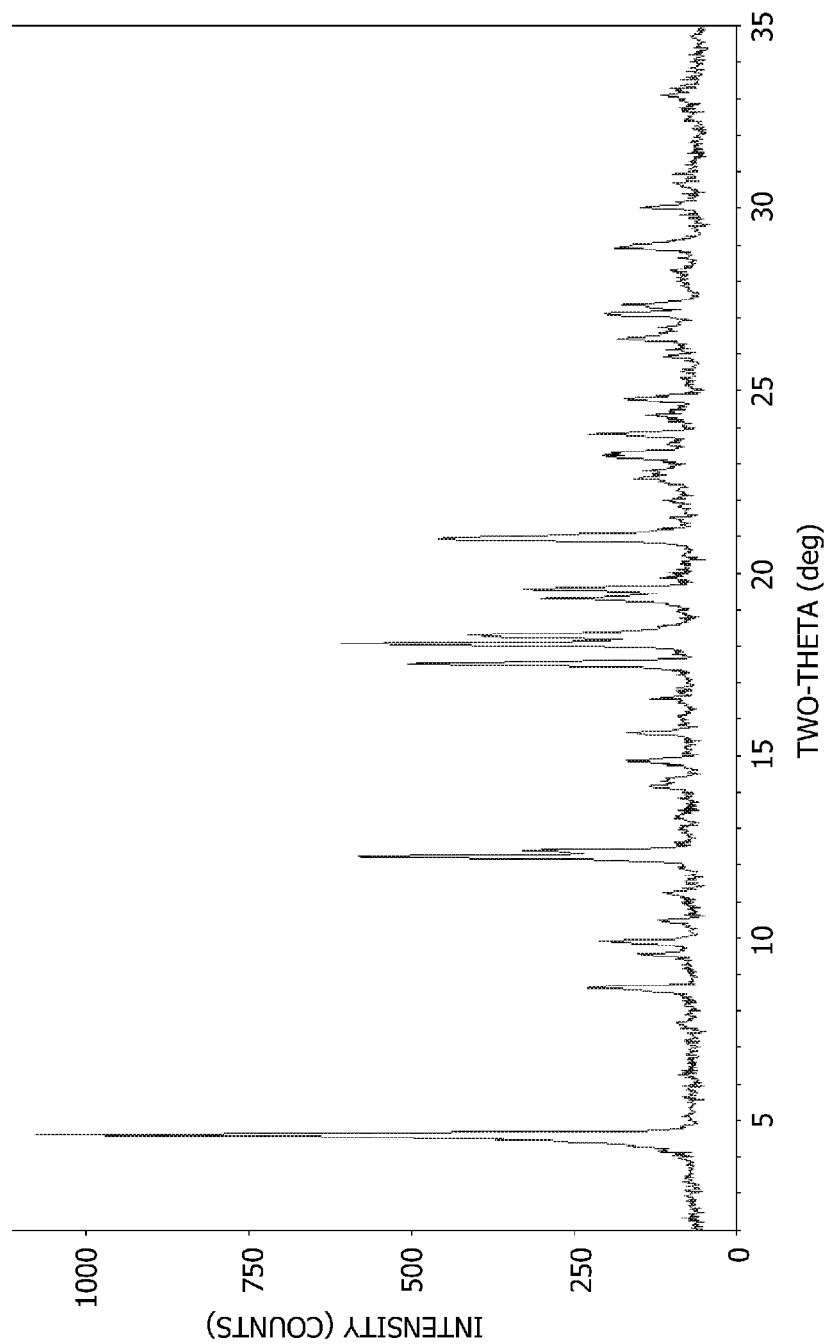
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**FIG. 12**

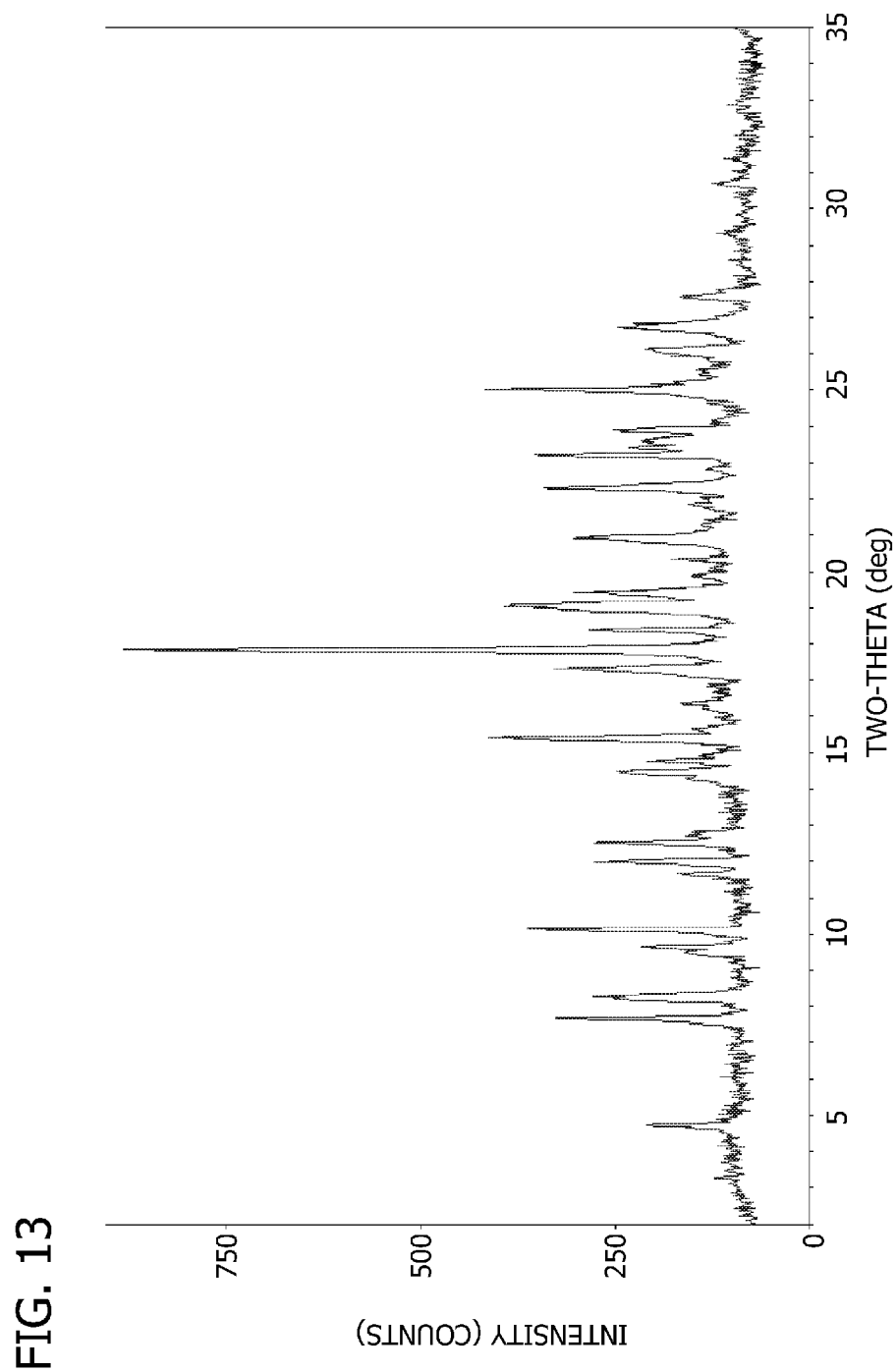


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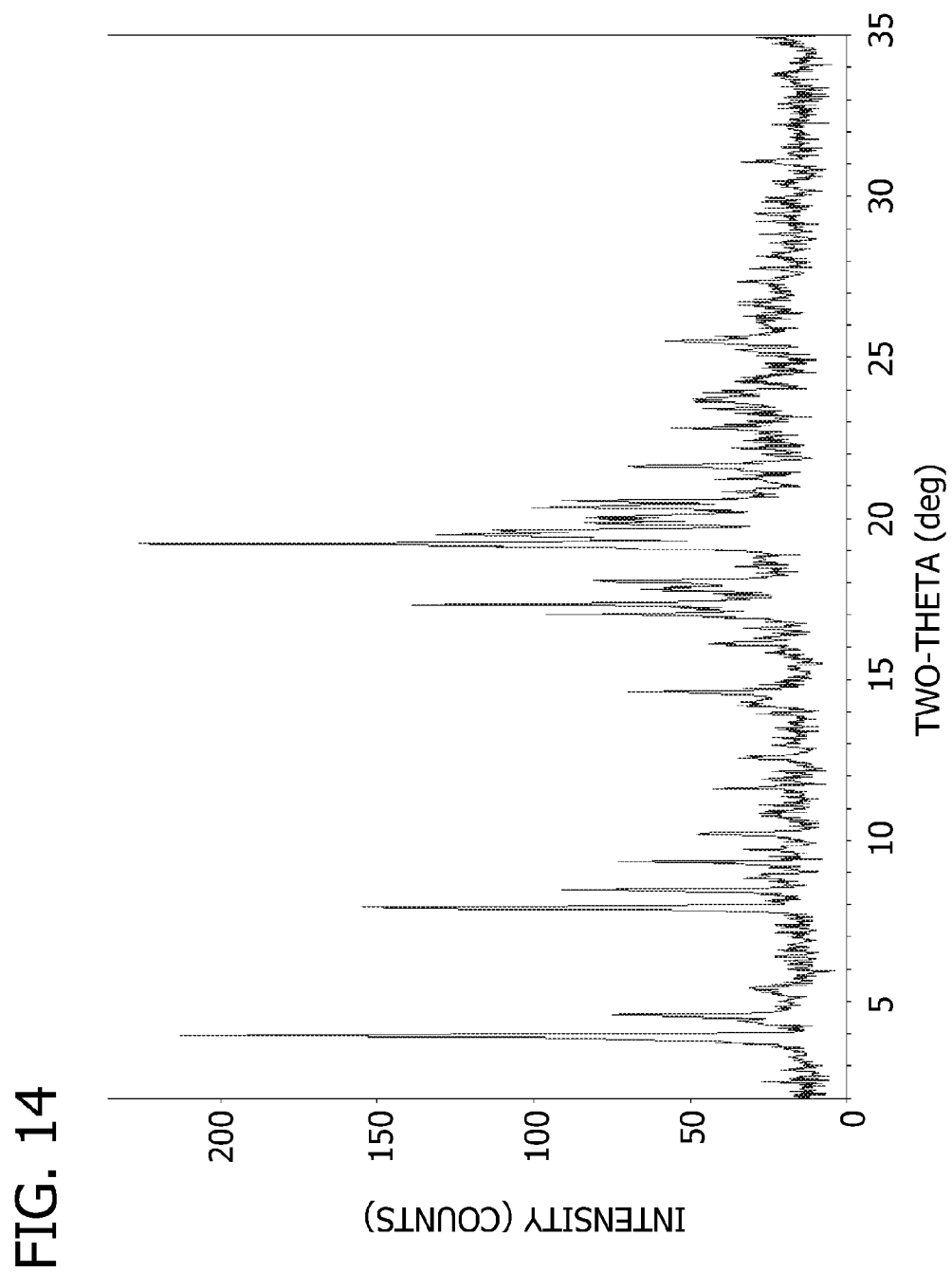


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## SALTS AND CRYSTALLINE FORMS OF AN APOPTOSIS-INDUCING AGENT

### CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of provisional application Ser. No. 61/416,656, filed Nov. 23, 2010, which is hereby incorporated by reference as if set forth in its entirety.

Cross-reference is also made, without claim to benefit of priority or admission as to prior art status, to the following pending U.S. application containing subject matter related to the present application: Ser. No. 12/787,682 (published as U.S. 2010/0305122) titled "Apoptosis-inducing Agents for the Treatment of Cancer and Immune and Autoimmune Diseases," the entire disclosure of which is incorporated herein by reference.

### FIELD OF THE INVENTION

The present invention relates to salts and crystalline forms of an apoptosis-inducing agent, to pharmaceutical dosage forms comprising such salts and crystalline forms, to processes for preparing salts and crystalline forms, and to methods of use thereof for treating diseases characterized by over-expression of anti-apoptotic Bcl-2 family proteins.

### BACKGROUND OF THE INVENTION

Overexpression of Bcl-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system.

Evasion of apoptosis is a hallmark of cancer (Hanahan & Weinberg (2000) *Cell* 100:57-70). Cancer cells must overcome a continual bombardment by cellular stresses such as DNA damage, oncogene activation, aberrant cell cycle progression and harsh microenvironments that would cause normal cells to undergo apoptosis. One of the primary means by which cancer cells evade apoptosis is by up-regulation of anti-apoptotic proteins of the Bcl-2 family.

A particular type of neoplastic disease for which improved therapies are needed is non-Hodgkin's lymphoma (NHL). NHL is the sixth most prevalent type of new cancer in the U.S. and occurs primarily in patients 60-70 years of age. NHL is not a single disease but a family of related diseases, which are classified on the basis of several characteristics including clinical attributes and histology.

One method of classification places different histological subtypes into two major categories based on natural history of the disease, i.e., whether the disease is indolent or aggressive. In general, indolent subtypes grow slowly and are generally incurable, whereas aggressive subtypes grow rapidly and are potentially curable. Follicular lymphomas are the most common indolent subtype, and diffuse large-cell lymphomas constitute the most common aggressive subtype. The oncoprotein Bcl-2 was originally described in non-Hodgkin's B-cell lymphoma.

Treatment of follicular lymphoma typically consists of biologically-based or combination chemotherapy. Combination therapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is routinely used, as is combination therapy with rituximab, cyclophosphamide, vincristine and prednisone (RCVP). Single-agent therapy with rituximab (targeting CD20, a phosphoprotein uniformly expressed on the surface of B-cells) or fludarabine

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is also used. Addition of rituximab to chemotherapy regimens can provide improved response rate and increased progression-free survival.

Radioimmunotherapy agents, high-dose chemotherapy and stem cell transplants can be used to treat refractory or relapsed NHL. Currently, there is not an approved treatment regimen that produces a cure, and current guidelines recommend that patients be treated in the context of a clinical trial, even in a first-line setting.

First-line treatment of patients with aggressive large B-cell lymphoma typically consists of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), or dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R).

Most lymphomas respond initially to any one of these therapies, but tumors typically recur and eventually become refractory. As the number of regimens patients receive increases, the more chemotherapy-resistant the disease becomes. Average response to first-line therapy is approximately 75%, 60% to second-line, 50% to third-line, and about 35-40% to fourth-line therapy. Response rates approaching 20% with a single agent in a multiple relapsed setting are considered positive and warrant further study.

Other neoplastic diseases for which improved therapies are needed include leukemias such as chronic lymphocytic leukemia (like NHL, a B-cell lymphoma) and acute lymphocytic leukemia.

Chronic lymphoid leukemia (CLL) is the most common type of leukemia. CLL is primarily a disease of adults, more than 75% of people newly diagnosed being over the age of 50, but in rare cases it is also found in children. Combination chemotherapies are the prevalent treatment, for example fludarabine with cyclophosphamide and/or rituximab, or more complex combinations such as CHOP or R-CHOP.

Acute lymphocytic leukemia, also known as acute lymphoblastic leukemia (ALL), is primarily a childhood disease, once with essentially zero survival but now with up to 75% survival due to combination chemotherapies similar to those mentioned above. New therapies are still needed to provide further improvement in survival rates.

Current chemotherapeutic agents elicit their antitumor response by inducing apoptosis through a variety of mechanisms. However, many tumors ultimately become resistant to these agents. Bcl-2 and Bcl-X<sub>L</sub> have been shown to confer chemotherapy resistance in short-term survival assays in vitro and, more recently, in vivo. This suggests that if improved therapies aimed at suppressing the function of Bcl-2 and Bcl-X<sub>L</sub> can be developed, such chemotherapy-resistance could be successfully overcome.

Involvement of Bcl-2 proteins in bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, CLL, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer, spleen cancer and the like is described in International Patent Publication Nos. WO 2005/024636 and WO 2005/049593.

Involvement of Bcl-2 proteins in immune and autoimmune diseases is described, for example, by Puck & Zhu (2003) *Current Allergy and Asthma Reports* 3:378-384; Shimazaki et al. (2000) *British Journal of Haematology* 110(3):584-590; Rengan et al. (2000) *Blood* 95(4):1283-1292; and Holzelova et al. (2004) *New England Journal of Medicine* 351(14):1409-1418. Involvement of Bcl-2 proteins in bone marrow

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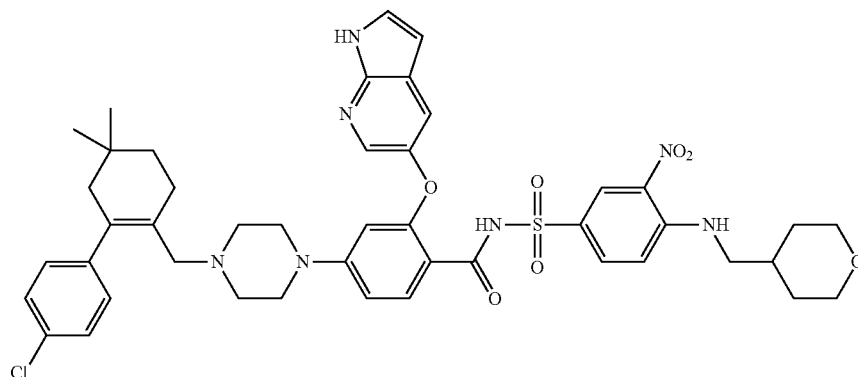
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transplant rejection is disclosed in United States Patent Application Publication No. US 2008/0182845.

Compounds that occupy a binding site on Bcl-2 proteins are known. To be therapeutically useful by oral administra-

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methyl]piperazin-1-yl)-N-(3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide, and which can be depicted by the formula:



tion, such compounds desirably have high binding affinity, exhibiting for example  $K_i < 1$  nM, preferably  $< 0.1$  nM, more preferably  $< 0.01$  nM, to proteins of the Bcl-2 family, specifically Bcl-2, Bcl-X<sub>L</sub> and Bcl-w. It is further desirable that they be formulated in a manner that provides high systemic exposure after oral administration. A typical measure of systemic exposure after oral administration of a compound is the area under the curve (AUC) resulting from graphing plasma concentration of the compound versus time from oral administration.

Apoptosis-inducing drugs that target Bcl-2 family proteins such as Bcl-2 and Bcl-X<sub>L</sub> are best administered according to a regimen that provides continual, for example daily, replenishment of the plasma concentration, to maintain the concentration in a therapeutically effective range. This can be achieved by daily parenteral, e.g., intravenous (i.v.) or intraperitoneal (i.p.) administration. However, daily parenteral administration is often not practical in a clinical setting, particularly for outpatients. To enhance clinical utility of an apoptosis-inducing agent, for example as a chemotherapeutic in cancer patients, a dosage form with acceptable oral bioavailability would be highly desirable. Such a dosage form, and a regimen for oral administration thereof, would represent an important advance in treatment of many types of cancer, including NHL, CLL and ALL, and would more readily enable combination therapies with other chemotherapeutics.

Different crystalline forms of an apoptosis-inducing agent can provide different properties with respect to stability, solubility, dissolution rate, hardness, compressibility and melting point, among other physical and mechanical properties. Because ease of manufacture, formulation, storage and transport of an apoptosis-inducing agent is dependent on at least some of these properties, there is a need in the chemical and therapeutic arts for identification of new salts and crystalline forms of apoptosis-inducing agents and ways for reproducibly generating such salts and crystalline forms.

#### SUMMARY OF THE INVENTION

The present disclosure relates to salts and crystalline forms of an apoptosis-inducing agent, referred to herein as "Compound 1," which has the systematic name 4-(4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]

Following synthesis of Compound 1, as described herein, the product may be recovered as a powder in an amorphous state. An amorphous form of Compound 1 may not be well suited for use as an active pharmaceutical ingredient (API) for various types of downstream formulations. More particularly, an amorphous form of Compound 1 can be difficult and therefore expensive to purify and can present process control problems.

The present disclosure provides a series of novel salts and crystalline forms of Compound 1 suitable for use as API in a wide variety of formulation types, including those where the API is present in particulate form together with excipients, for example in orally deliverable tablets or capsules. The salts and crystalline forms of Compound 1 may also be useful where the crystalline form is converted to a non-crystalline form (e.g., solution or amorphous form) when formulated. Also included are ways to prepare the salts and crystalline forms of Compound 1. Salt and crystalline forms of Compound 1 can be used to modulate and/or improve the physicochemical properties of the API, including solid state properties (e.g., crystallinity, hygroscopicity, melting point, hydration potential, polymorphism, etc.), pharmaceutical properties (e.g., solubility/dissolution rate, stability, compatibility, etc.), and crystallization characteristics (e.g., purity, yield, morphology, etc.), as non-limiting examples.

In some embodiments, the salt or crystalline form of Compound 1 includes those of Compound 1 free base anhydrate having PXRD pattern A, Compound 1 free base anhydrate having PXRD pattern B, Compound 1 free base hydrate having PXRD pattern C, Compound 1 free base hydrate having PXRD pattern D, Compound 1 free base dichloromethane solvate having pattern E, Compound 1 free base ethyl acetate solvate having PXRD pattern F, Compound 1 free base ethyl acetate solvate having PXRD pattern G, Compound 1 free base acetonitrile solvate having PXRD pattern H, Compound 1 free base acetonitrile solvate having PXRD pattern I, Compound 1 free base acetone solvate having PXRD pattern J, Compound 1 hydrochloride having PXRD pattern K, Compound 1 hydrochloride hydrate having PXRD pattern L, Compound 1 sulfate having PXRD pattern M, and Compound 1 free base tetrahydrofuran (THF) solvate having PXRD pattern N, each having the respective powder X-ray diffraction patterns as described herein.

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In some embodiments, the crystalline forms of Compound 1 free base dichloromethane solvate, Compound 1 free base acetonitrile solvate, Compound 1 hydrochloride, and Compound 1 free base tetrahydrofuran solvate have the respective crystal lattice parameters as described herein.

In another embodiment, Compound 1 hydrochloride is provided.

In another embodiment, Compound 1 sulfate is provided.

In some embodiments, an API composition is provided comprising Compound 1 as the API, in which at least a portion, for example at least about 10%, of the Compound 1 in the composition is in a salt or crystalline form. In some embodiments, greater than 95% or essentially 100% of the API in such a composition is a salt or crystalline form of Compound 1.

In some embodiments, a pharmaceutical composition is provided that comprises a salt or crystalline form of Compound 1 as described herein and one or more pharmaceutically acceptable excipients.

In some embodiments, a process for preparing a pharmaceutical solution composition of Compound 1 is provided, where the process comprises dissolving a salt or crystalline form of Compound 1 as described herein with a pharmaceutically acceptable solvent or mixture of solvents.

In some embodiments, a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein is provided, where the method comprises administering to a subject having the disease a therapeutically effective amount of (a) a salt or crystalline form of Compound 1 as described herein or (b) a pharmaceutical composition comprising a salt or crystalline form of Compound 1 as described herein and one or more pharmaceutically acceptable excipients.

In some embodiments, a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein is provided, where the method comprises preparing a solution or dispersion of a salt or crystalline form of Compound 1 described herein in a pharmaceutically acceptable solvent or mixture of

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## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a PXRD scan of Compound 1 anhydrate designated pattern A.

FIG. 2 is a PXRD scan of Compound 1 anhydrate designated pattern B.

FIG. 3 is a PXRD scan of Compound 1 hydrate designated pattern C.

FIG. 4 is a PXRD scan of Compound 1 hydrate designated pattern D.

FIG. 5 is a calculated PXRD pattern of Compound 1 dichloromethane solvate designated pattern E.

FIG. 6 is a PXRD scan of Compound 1 ethyl acetate solvate designated pattern F.

FIG. 7 is a PXRD scan of Compound 1 ethyl acetate solvate designated pattern G.

FIG. 8 is a calculated PXRD pattern of Compound 1 acetonitrile solvate designated pattern H.

FIG. 9 is a PXRD scan of Compound 1 acetonitrile solvate designated pattern I.

FIG. 10 is a PXRD scan of Compound 1 acetone solvate designated pattern J.

FIG. 11 is a calculated PXRD pattern of Compound 1 hydrochloride designated pattern K.

FIG. 12 is a PXRD scan of Compound 1 hydrochloride hydrate designated pattern L.

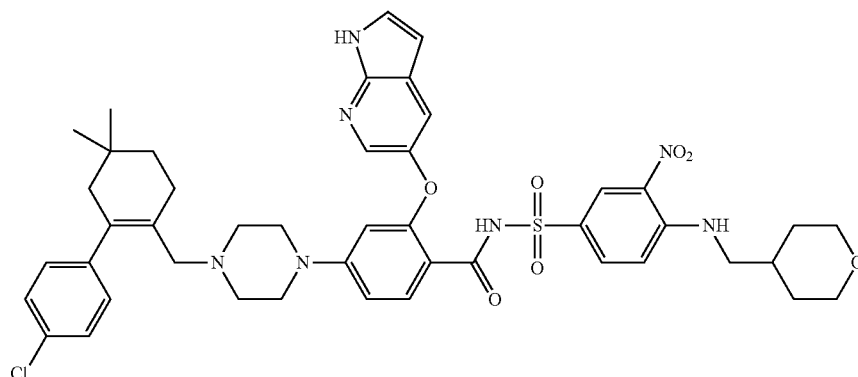
FIG. 13 is a PXRD scan of Compound 1 sulfate designated pattern M.

FIG. 14 is a PXRD scan of Compound 1 tetrahydrofuran solvate designated pattern N.

## DETAILED DESCRIPTION

The term "free base" is used for convenience herein to refer to Compound 1 parent compound as distinct from any salt thereof, while recognizing that the parent compound, strictly speaking, is zwitterionic at neutral conditions and thus does not always behave as a true base.

An apoptosis-inducing agent, referred to herein as Compound 1, has the systematic name 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide, and can be depicted by the formula:



solvents, and administering the resulting solution or dispersion in a therapeutically effective amount to a subject having the disease.

Additional embodiments of the invention, including particular aspects of those provided above, will be found in, or will be evident from, the detailed description that follows.

In various embodiments, salts and crystalline forms of Compound 1 are provided. Crystalline forms include solvates, hydrates, anhydrides, and salts of Compound 1.

In contrast to an amorphous form of Compound 1 free base and an amorphous form of a Compound 1 salt, a crystalline form is characterized by the presence of observable peaks in a powder x-ray diffraction (PXRD) pattern measured on the



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crystalline form. For crystalline forms prepared to yield suitably sized single-crystals, the crystalline form can be further characterized through an experimental determination of the unit cell parameters, the identification of the crystallographic space group to which a single crystal belongs, or both of these. Once the unit cell parameters are known, the location of the diffraction peaks, and in particular the  $2\theta$  values of the peaks in a PXRD pattern can be calculated, to further characterize the crystalline form. Of course, the PXRD pattern can also be measured experimentally for such crystalline forms. If not only the cell parameters but a three dimensional single crystal structure is known, then not only the positions but also the intensity of the peaks in the diffraction pattern can be calculated in further characterization of the crystalline form.

The PXRD patterns measured or calculated for the salts and crystalline forms reported herein represent a fingerprint that can be compared to other experimentally determined patterns to find a match. Identity of the respective crystalline forms is established by overlap or match of an experimentally determined PXRD pattern with the PXRD pattern of the crystalline forms reported herein. In various embodiments, the salts and crystalline forms are characterized by exhibiting at least one of the PXRD peaks reported here. Thus, in various embodiments, a salt or crystalline form is characterized by a match of two or more peaks, a match of 3 or more peaks, 4 or more peaks, or 5 or more peaks, and so on, from the respective PXRD patterns.

An embodiment of the synthesis of Compound 1 (free base) and representative intermediate compounds is presented below. The exemplified compounds are named using ACD/ChemSketch Version 5.06 (5 Jun. 2001, Advanced Chemistry Development Inc., Toronto, Ontario), ACD/ChemSketch Version 12.01 (13 May 2009), Advanced Chemistry Development Inc., Toronto, Ontario), or ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, Mass.). Intermediates are named using ChemDraw® Ver. 9.0.5 (CambridgeSoft, Cambridge, Mass.).

#### Synthesis of Compound 1

4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl)piperazin-1-yl)-N-([3-nitro-4-((tetrahydro-2H-pyran-4-yl)methyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

#### Compound A

3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino)benzenesulfonamide

A mixture of 4-fluoro-3-nitrobenzenesulfonamide (2.18 g), 1-(tetrahydropyran-4-yl)methylamine (1.14 g), and triethylamine (1 g) in tetrahydrofuran (30 mL) were stirred overnight, neutralized with concentrated HCl and concentrated. The residue was suspended in ethyl acetate and the precipitates were collected, washed with water and dried to provide the title compound.

#### Compound B

methyl 4,4-dimethyl-2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate

To a suspension of hexane washed NaH (17 g) in dichloromethane (700 mL) was added 5,5-dimethyl-2-methoxycar-

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bonylcyclohexanone (38.5 g) dropwise at 0° C. After stirring for 30 minutes, the mixture was cooled to -78° C. and trifluoroacetic anhydride (40 mL) was added. The reaction mixture was warmed to room temperature and stirred for 24 hours. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give the product.

#### Compound C

methyl 2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enecarboxylate

Compound B (62.15 g), 4-chlorophenylboronic acid (32.24 g), CsF (64 g) and tetrakis(triphenylphosphine)palladium(0) (2 g) in 2:1 dimethoxyethane/methanol (600 mL) were heated to 70° C. for 24 hours. The mixture was concentrated. Ether (4×200 mL) was added and the mixture was filtered. The combined ether solution was concentrated to give the product.

#### Compound D

(2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methanol

To a mixture of LiBH<sub>4</sub> (13 g), Compound C (53.8 g) and ether (400 mL), was added methanol (25 mL) slowly by syringe. The mixture was stirred at room temperature for 24 hours. The reaction was quenched with 1N HCl with ice-cooling. The mixture was diluted with water and extracted with ether (3×100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

#### Compound E

tert-butyl 4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine-1-carboxylate

Mesyl Chloride (7.5 mL) was added via syringe to Compound D (29.3 g) and triethylamine (30 mL) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0° C., and the mixture was stirred for 1 minute. N-t-butoxycarbonylpiperazine (25 g) was added and the mixture was stirred at room temperature for 24 hours. The suspension was washed with brine, dried, (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10-20% ethyl acetate/hexanes.

#### Compound F

1-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazine

Compound E (200 mg) and triethylsilane (1 mL) were stirred in dichloromethane (15 mL) and trifluoroacetic acid (15 mL) for 1 hour. The mixture was concentrated, taken up in ethyl acetate, washed twice with NaH<sub>2</sub>PO<sub>4</sub>, and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated.

#### Compound G

5-bromo-1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridine

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine (15.4 g) in tetrahydrofuran (250 mL) was added 1M lithium hexamethyldisilazide in tetrahydrofuran (86 mL), and after 10

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minutes, TIPS-Cl (triisopropylchlorosilane) (18.2 mL) was added. The mixture was stirred at room temperature for 24 hours. The reaction was diluted with ether, and the resulting solution was washed twice with water. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 10% ethyl acetate/hexanes.

## Compound H

1-(triisopropylsilyl)-1H-pyrrolo[2,3-b]pyridin-5-ol

To a mixture of Compound G (24.3 g) in tetrahydrofuran (500 mL) at -78° C. was added 2.5M BuLi (30.3 mL). After 2 minutes, trimethylborate (11.5 mL) was added, and the mixture was allowed to warm to room temperature over 1 hour. The reaction was poured into water, extracted three times with ethyl acetate, and the combined extracts were washed with brine and concentrated. The crude product was taken up in tetrahydrofuran (200 mL) at 0° C., and 1M NaOH (69 mL) was added, followed by 30% H<sub>2</sub>O<sub>2</sub> (8.43 mL), and the solution was stirred for 1 hour. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 g) was added, and the pH was adjusted to 4-5 with concentrated HCl and solid NaH<sub>2</sub>PO<sub>4</sub>. The solution was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude product was chromatographed on silica gel with 5-25% ethyl acetate/hexanes.

## Compound I

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-fluorobenzoate

A mixture of Compound H (8.5 g), methyl 2,4-difluorobenzoate (7.05 g), and K<sub>3</sub>PO<sub>4</sub> (9.32 g) in diglyme (40 mL) at 115° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (600 mL), and washed twice with water, and brine, and concentrated. The crude product was chromatographed on silica gel with 2-50% ethyl acetate/hexanes.

## Compound J

methyl 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoate

A mixture of Compound I (1.55 g), Compound F (2.42 g), and HK<sub>2</sub>PO<sub>4</sub> (1.42 g) in dimethylsulfoxide (20 mL) at 135° C. was stirred for 24 hours. The reaction was cooled, diluted with ether (400 mL), and washed with 3× 1M NaOH, and brine, and concentrated. The crude product was chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## Compound K

2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid

Compound J (200 mg) in dioxane (10 mL) and 1M NaOH (6 mL) at 50° C. was stirred for 24 hours. The reaction was cooled, added to NaH<sub>2</sub>PO<sub>4</sub> solution, and extracted three times with ethyl acetate. The combined extracts were washed with brine, and concentrated to give the pure product.

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## Compound L

## Compound 1 Free Base

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide

Compound K (3.39 g), Compound A (1.87 g), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (2.39 g), and 4-dimethylaminopyridine (1.09 g) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) for 24 hours. The reaction was cooled and chromatographed on silica gel with 25-100% ethyl acetate/hexanes, then 10% methanol/ethyl acetate with 1% acetic acid, to give the product (1.62 g, 32%) as a solid. <sup>1</sup>H NMR (300 MHz, dimethylsulfoxide-d<sub>6</sub>) 11.65 (br s, 1H), 8.55 (br s, 1H), 8.04 (d, 1H), 7.89 (dd, 1H), 7.51 (m, 3H), 7.33 (d, 2H), 7.08 (m, 1H), 7.04 (d, 2H), 6.68 (dd, 1H), 6.39 (d, 1H), 6.19 (d, 1H), 3.84 (m, 1H), 3.30 (m, 4H), 3.07 (m, 4H), 2.73 (m, 2H), 2.18 (m, 6H), 1.95 (m, 2H), 1.61 (dd, 2H), 1.38 (m, 2H), 1.24 (m, 4H), 0.92 (s, 6H).

Preparation of Compound 1 free base is also described in Example 5 of U.S. application Ser. No. 12/787,682 (published as U.S. 2010/0305122) titled "Apoptosis-inducing agents for the treatment of cancer and immune and autoimmune diseases," the entire disclosure of which is incorporated herein by reference. A solid can be prepared from the chromatography eluate; for example, by using freeze-drying, precipitation, or rotary evaporation techniques. The product of this process can be a solid that is amorphous in character.

Salts and crystal forms of Compound 1 have been prepared as described in the following examples.

## Compound 1 Free Base Anhydrate

## PXRD Pattern A

The following two routes can prepare this crystalline form, where drying at ambient conditions involves leaving the solid material at room temperature and exposed to air overnight. For example, solvent can be allowed to evaporate.

## Example 1

Compound 1 free base dichloromethane solvate having pattern E (see below) was dried at ambient conditions.

## Example 2

Compound 1 free base ethyl acetate solvate having pattern F (see below) was dried at ambient conditions.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 1 and Table 1, respectively.

TABLE 1

Peak Listing for Compound 1 Free Base Anhydrate Pattern A  
Peak Position (° 2θ)

6.3  
7.1  
9.0  
9.5  
12.5  
14.5  
14.7

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TABLE 1-continued

| Peak Listing for Compound 1 Free Base Anhydrate Pattern A |
|---|
| Peak Position (° 2θ)                                      |
| 15.9  |
| 16.9  |
| 18.9  |

Compound 1 Free Base Anhydrate

PXRD Pattern B

Example 3

Compound 1 free base acetonitrile solvate pattern H was dried at ambient conditions.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 2 and Table 2, respectively.

TABLE 2

| Peak Listing for Compound 1 Free Base Anhydrate Pattern B |
|---|
| Peak Position (° 2θ)                                      |
| 5.8   |
| 7.7   |
| 8.3   |
| 9.9   |
| 13.0  |
| 13.3  |
| 14.2  |
| 15.3  |
| 16.6  |
| 17.9  |
| 18.3  |
| 19.8  |
| 20.7  |
| 21.2  |
| 21.9  |
| 22.5  |
| 23.6  |
| 24.1  |

Compound 1 Free Base Hydrate

PXRD Pattern C

The free base hydrate, characterized by Pattern C, can be prepared in three ways.

Example 4

Compound 1 free base methanol solvate was dried at ambient conditions.

Example 5

Compound 1 Free Base Ethanol Solvate was Dried at Ambient Conditions.

Example 6

Compound 1 free base 2-propanol solvate was dried at ambient Conditions.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 3 and Table 3, respectively.

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TABLE 3

| Peak Listing for Compound 1 Free Base Hydrate Pattern C |
|---|
| Peak Position (° 2θ)                                    |
| 5.8   |
| 7.6   |
| 7.9   |
| 10.7  |
| 11.7  |
| 14.0  |
| 15.3  |
| 15.8  |
| 17.4  |
| 18.3  |
| 19.9  |
| 20.4  |
| 20.7  |
| 22.5  |
| 24.9  |
| 25.8  |
| 26.7  |

Compound 1 Free Base Hydrate

PXRD Pattern D

Example 7

Compound 1 Free Base Ethyl Acetate Solvate Pattern G was Dried at Ambient Conditions.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 4 and Table 4, respectively.

TABLE 4

| Peak Listing for Compound 1 Free Base Hydrate Pattern D |
|---|
| Peak Position (° 2θ)                                    |
| 3.3   |
| 6.4   |
| 7.1   |
| 7.3   |
| 10.1  |
| 11.4  |
| 13.2  |
| 14.4  |
| 14.6  |
| 15.1  |
| 15.8  |
| 16.2  |
| 17.2  |
| 17.6  |
| 18.0  |
| 18.6  |
| 19.0  |
| 19.5  |
| 19.8  |
| 20.2  |
| 20.7  |
| 21.0  |
| 22.5  |
| 23.0  |
| 26.0  |
| 28.9  |
| 29.2  |

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## Compound 1 Free Base Dichloromethane Solvate

## PXRD Pattern E

## Example 8

Compound 1 free base solid was suspended in dichloromethane at ambient temperatures to reach its solubility. After equilibrating, the solids were isolated at ambient temperature.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 5 and Table 5A, respectively. Crystallographic information is listed in Table 5B.

TABLE 5A

| Calculated PXRD Peak Listing for Compound 1 Free Base Dichloromethane Solvate Pattern E<br>Peak Position (° 2θ) |      |
|---|------|
|   | 5.9  |
|   | 7.1  |
|   | 9.6  |
|   | 10.0 |
|   | 10.7 |
|   | 11.1 |
|   | 13.2 |
|   | 14.8 |
|   | 18.2 |

TABLE 5B

| Structural Information for Compound 1 Free Base Dichloromethane Solvate Single Crystal |  |
|--|--|
| Crystal Form   | Compound 1 Free Base Dichloromethane Solvate |
| Lattice Type   | Monoclinic                                   |
| Space Group  | P21/n  |
| a (Å)  | 13.873                                       |
| b (Å)  | 12.349                                       |
| c (Å)  | 29.996                                       |
| α (°)  | 90.00  |
| β (°)  | 92.259                                       |
| γ (°)  | 90.00  |
| Volume (Å <sup>3</sup> )   | 5134.85                                      |
| Z  | 4  |

Compound 1 Free Base Ethyl Acetate Solvate (PXRD Pattern F)

## Example 9

Compound 1 free base solid was suspended in ethyl acetate at ambient temperatures to reach its solubility. After equilibrating, the solids were isolated at ambient temperature.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 6 and Table 6, respectively.

TABLE 6

| PXRD Peak Listing for Compound 1 Free Base Ethyl Acetate Solvate Pattern F<br>Peak Position (° 2θ) |      |
|--|------|
|  | 5.8  |
|  | 7.1  |
|  | 9.5  |
|  | 9.9  |
|  | 10.6 |
|  | 11.6 |

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## TABLE 6-continued

PXRD Peak Listing for Compound 1 Free Base Ethyl Acetate Solvate Pattern F  
Peak Position (° 2θ)

13.1  
13.8  
14.8  
16.0  
17.9  
20.2  
21.2  
23.2  
24.4  
26.4

Compound 1 Free Base Ethyl Acetate Solvate (PXRD Pattern G)

## Example 10

Compound 1 free base solid was suspended in ethyl acetate saturated with water at ambient temperatures to reach its solubility. After equilibrating, the solids were isolated at ambient temperature.

Powder X-ray diffraction pattern and peak listing shown in FIG. 7 and Table 7, respectively.

TABLE 7

| PXRD Peak Listing for Compound 1 Free Base Ethyl Acetate Solvate Pattern G<br>Peak Position (° 2θ) |      |
|--|------|
|  | 3.3  |
|  | 6.5  |
|  | 7.0  |
|  | 7.3  |
|  | 9.2  |
|  | 9.7  |
|  | 11.2 |
|  | 11.4 |
|  | 11.9 |
|  | 12.9 |
|  | 14.4 |
|  | 14.9 |
|  | 15.8 |
|  | 16.2 |
|  | 17.2 |
|  | 17.4 |
|  | 17.8 |
|  | 18.5 |
|  | 18.9 |
|  | 19.4 |
|  | 20.1 |
|  | 20.7 |
|  | 20.9 |
|  | 22.0 |
|  | 22.7 |
|  | 23.4 |
|  | 23.8 |
|  | 24.7 |
|  | 25.9 |
|  | 27.0 |
|  | 28.9 |

## Compound 1 Free Base Acetonitrile Solvate

## PXRD Pattern H

## Example 11

Compound 1 free base solid was suspended in acetonitrile at ambient temperatures to reach its solubility. After equilibrating, the solids were isolated at ambient temperature.



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Powder X-ray diffraction pattern and peak listing are shown in FIG. 8 and Table 8A, respectively. Crystallographic information is listed in Table 8B.

TABLE 8A

| Calculated PXRD Peak Listing for Compound 1<br>Free Base Acetonitrile Solvate Pattern H<br>Peak Position (° 2θ) |  |
|---|--|
| 5.8   |  |
| 7.4   |  |
| 7.6   |  |
| 10.2  |  |
| 13.0  |  |
| 13.6  |  |
| 14.9  |  |
| 16.4  |  |
| 17.0  |  |
| 17.5  |  |
| 18.2  |  |
| 19.4  |  |
| 19.7  |  |
| 20.4  |  |
| 21.0  |  |
| 21.2  |  |
| 21.8  |  |
| 22.4  |  |
| 22.9  |  |
| 24.2  |  |
| 24.3  |  |
| 26.1  |  |
| 29.2  |  |

TABLE 8B

| Structural information for Compound 1 Free<br>Base Acetonitrile Solvate H Single Crystal |  |
|--|--|
| Crystal Form   | Compound 1 Free Base<br>Acetonitrile Solvate A |
| Lattice Type   | Triclinic                                      |
| Space Group  | P1   |
| a (Å)  | 12.836   |
| b (Å)  | 13.144   |
| c (Å)  | 15.411   |
| α (°)  | 92.746   |
| β (°)  | 95.941   |
| γ (°)  | 113.833  |
| Volume (Å <sup>3</sup> )   | 2354.06  |
| Z  | 2  |

Compound 1 Free Base Acetonitrile Solvate (PXRD Pattern I)

## Example 12

To a solution of 2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-4-((4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-enyl)methyl)piperazin-1-yl)benzoic acid (16 g, 28 mmol) and 3-nitro-4-((tetrahydro-2H-pyran-4-yl)methylamino) benzenesulfonamide (8.83 g, 28 mmol) in DCM (300 mL) was added EDCI (10.74 g, 56 mmol) and DMAP (6.85 g, 56 mmol). The mixture was stirred at r.t. overnight. LC/MS showed the expected product as a single peak. The mixture was diluted with DCM (500 ml) and washed with aq. NaHCO<sub>3</sub>, water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The residue after evaporation of solvent was dissolved in DCM and loaded on a column and eluted with 30% ethyl acetate in DCM followed by 1 to 2% MeOH in DCM to give 24.5 g pure product (95% purity) which was dissolved in DMSO and MeOH (1:1) and TFA (2 eq) and loaded on a 330 g C18 column (6 g a time) to give 13.5 g pure (>99.7% purity)

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product (55% yield). The API was extracted using dichloromethane and then, the solvent was removed using rotary evaporator. The resulting solid was suspended in acetonitrile at ambient temperatures to reach its solubility. After equilibrating, the solids were isolated at ambient temperature.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 9 and Table 9, respectively.

TABLE 9

| PXRD Peak Listing for Compound 1 Free<br>Base Acetonitrile Solvate Pattern I<br>Peak Position (° 2θ) |  |
|--|--|
| 6.4  |  |
| 6.9  |  |
| 7.7  |  |
| 8.8  |  |
| 9.4  |  |
| 11.1   |  |
| 12.3   |  |
| 12.8   |  |
| 16.5   |  |
| 17.0   |  |
| 17.4   |  |
| 18.3   |  |
| 18.6   |  |
| 19.0   |  |
| 19.2   |  |
| 20.3   |  |
| 21.6   |  |
| 22.3   |  |
| 22.9   |  |
| 23.7   |  |

Compound 1 Free Base Acetone Solvate

PXRD Pattern J

## Example 13

Compound 1 free base solid was suspended in acetone at ambient temperatures to reach its solubility. After equilibrating, the solids were isolated at ambient temperature.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 10 and Table 10, respectively.

TABLE 10

| PXRD Peak Listing for Compound 1 Free Base Acetone Solvate Pattern J<br>Peak Position (° 2θ) |  |
|--|--|
| 6.0  |  |
| 6.8  |  |
| 8.0  |  |
| 9.0  |  |
| 9.7  |  |
| 11.2   |  |
| 11.9   |  |
| 12.6   |  |
| 14.7   |  |
| 15.0   |  |
| 15.2   |  |
| 15.8   |  |
| 16.4   |  |
| 16.6   |  |
| 17.6   |  |
| 17.8   |  |
| 17.9   |  |
| 18.7   |  |
| 20.2   |  |
| 20.8   |  |
| 21.6   |  |
| 22.2   |  |
| 22.6   |  |

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TABLE 10-continued

| PXRD Peak Listing for Compound 1 Free Base Acetone Solvate Pattern J<br>Peak Position (° 2θ) |      |
|--|------|
|  | 23.3 |
|  | 23.8 |
|  | 24.0 |
|  | 24.4 |
|  | 26.8 |
|  | 27.1 |
|  | 28.0 |
|  | 28.2 |

Compound 1 Hydrochloride

PXRD Pattern K

Example 14

Compound 1 free base solid (16 mg, 0.018 mmol) was suspended in 0.5 mL of acetonitrile. Hydrochloric acid (1M, 25  $\mu$ L) was added to the suspension while stirring (molar ratio of Compound 1:acid=1:1.4). Compound 1 quickly reacted with hydrochloric acid and formed a clear solution. Yellowish solids, which later crystallized from the solution, were confirmed to be Compound 1 hydrochloride in a 1:1 stoichiometric ratio of free base to HCl.

Powder X-ray diffraction pattern and peak listing can be seen in FIG. 11, and Table 11A, respectively. Crystallographic information is listed in Table 11B.

TABLE 11A

| Calculated PXRD Peak Listing of Compound 1 Hydrochloride Pattern K<br>Peak Position (° 2θ) |      |
|--|------|
|  | 5.1  |
|  | 5.9  |
|  | 7.7  |
|  | 9.9  |
|  | 10.2 |
|  | 10.8 |
|  | 13.6 |
|  | 14.0 |
|  | 15.4 |
|  | 15.9 |
|  | 16.2 |
|  | 17.6 |
|  | 18.3 |
|  | 18.7 |
|  | 19.7 |
|  | 19.9 |
|  | 20.1 |
|  | 20.4 |
|  | 20.7 |
|  | 20.9 |
|  | 22.9 |
|  | 26.2 |

TABLE 11B

| Structural information for Compound 1 Hydrochloride |                          |
|---|--------------------------|
| Crystal Form  | Compound 1 Hydrochloride |
| Lattice Type  | Triclinic                |
| Space Group   | P1                       |
| a (Å)   | 10.804                   |
| b (Å)   | 12.372                   |
| c (Å)   | 19.333                   |
| $\alpha$ (°)  | 76.540                   |

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TABLE 11B-continued

| Structural information for Compound 1 Hydrochloride |                          |
|---|--------------------------|
| Crystal Form  | Compound 1 Hydrochloride |
| $\beta$ (°)   | 87.159                   |
| $\gamma$ (°)  | 70.074                   |
| Volume (Å <sup>3</sup> )                            | 2361.5                   |
| Z   | 2                        |

Compound 1 Hydrochloride Hydrate

PXRD Pattern L

Example 15

Compound 1 hydrochloride solid (having pattern K) was exposed to the air under ambient conditions, and was confirmed to be Compound 1 hydrochloride hydrate.

Powder X-ray diffraction pattern and peak listing can be seen in FIG. 12, and Table 12, respectively.

TABLE 12

| PXRD Peak Listing for Compound 1 Hydrochloride Hydrate Pattern L<br>Peak Position (° 2θ) |      |
|--|------|
|  | 4.6  |
|  | 8.7  |
|  | 9.6  |
|  | 9.9  |
|  | 12.3 |
|  | 14.9 |
|  | 15.7 |
|  | 17.6 |
|  | 18.1 |
|  | 18.4 |
|  | 19.3 |
|  | 19.6 |
|  | 21.0 |
|  | 23.3 |
|  | 23.9 |
|  | 24.8 |
|  | 26.5 |
|  | 27.2 |
|  | 27.4 |
|  | 29.0 |
|  | 30.1 |

Compound 1 Sulfate

PXRD Pattern M

Example 16

Compound 1 free base solid (16 mg, 0.018 mmol) was suspended in 0.5 mL of 2-propanol at 70° C. Sulfuric acid (1M, 25  $\mu$ L) was added to the suspension while stirring (molar ratio of Compound 1:acid=1:1.4). Compound 1 quickly dissolved by reacting with sulfuric acid. Yellowish solids crystallized from the solution immediately after the dissolution occurred. The crystalline solid was confirmed to be Compound 1 sulfate with a stoichiometry of 1:1 using ion chromatography.

Powder X-ray diffraction pattern and peak listing can be seen in FIG. 13, and Table 13, respectively.

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TABLE 13

| PXRD Peak Listing for Compound 1 Sulfate Pattern M |  |
|--|--|
| Peak Position (° 2 $\theta$ )                      |  |
| 4.8  |  |
| 7.7  |  |
| 8.3  |  |
| 9.7  |  |
| 10.2   |  |
| 12.0   |  |
| 12.6   |  |
| 14.5   |  |
| 15.4   |  |
| 17.4   |  |
| 17.9   |  |
| 18.4   |  |
| 19.1   |  |
| 19.5   |  |
| 21.0   |  |
| 22.4   |  |
| 23.3   |  |
| 23.9   |  |
| 25.1   |  |
| 26.8   |  |

Compound 1 Free Base THF Solvate

PXRD Pattern N

Example 17

Compound 1 free base solid was suspended in tetrahydrofuran (THF) at ambient temperatures to reach its solubility. After equilibrating, the solids were isolated at ambient temperature.

Powder X-ray diffraction pattern and peak listing are shown in FIG. 14 and Table 14, respectively.

TABLE 14

| PXRD Peak Listing for Compound 1 Free Base THF Solvate Pattern N |  |
|--|--|
| Peak Position (° 2 $\theta$ )                                    |  |
| 4.0  |  |
| 4.6  |  |
| 8.0  |  |
| 8.5  |  |
| 9.4  |  |
| 14.6   |  |
| 17.1   |  |
| 17.4   |  |
| 17.8   |  |
| 18.1   |  |
| 19.2   |  |
| 19.5   |  |
| 20.1   |  |
| 20.4   |  |
| 20.5   |  |
| 21.7   |  |

PXRD data were collected using a G3000 diffractometer (Inel Corp., Ardenay, France) equipped with a curved position-sensitive detector and parallel-beam optics. The diffractometer was operated with a copper anode tube (1.5 kW fine focus) at 40 kV and 30 mA. An incident-beam germanium monochromator provided monochromatic radiation Cu—K $\alpha$  radiation, which has a wavelength of 1.54178 Å. The diffractometer was calibrated using the attenuated direct beam at one-degree intervals. Calibration was checked using a silicon powder line position reference standard (NIST 640c). The instrument was computer-controlled using Symphonix software (Inel Corp., Ardenay, France) and the data were analyzed using Jade software (version 6.5, Materials Data, Inc., Liver-

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more, Calif.). The sample was loaded onto an aluminum sample holder and leveled with a glass slide. PXRD peak position measurements are typically  $\pm 0.2$  degrees two-theta (° 2 $\theta$ ).

In some embodiments, the percent crystallinity of any of the salt or crystalline forms of Compound 1 described herein can vary with respect to the total amount of Compound 1. In particular, certain embodiments provide for the percent crystallinity of a salt or crystalline form of Compound 1 being at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99%. In some embodiments, the percent crystallinity can be substantially 100%, where substantially 100% indicates that the entire amount of Compound 1 appears to be crystalline as best can be determined using methods known in the art. Accordingly, pharmaceutical compositions and therapeutically effective amounts of Compound 1 can include amounts that vary in crystallinity. These include instances where Compound 1 is used as API in various formulations and solid forms, including where an amount of Compound 1 in a solid form is subsequently dissolved, partially dissolved, or suspended or dispersed in a liquid.

As noted, in some embodiments API compositions are provided that comprise Compound 1, wherein at least a portion of the Compound 1 in the API composition is in one of the salt or crystalline forms. For example, an API composition containing Compound 1 has at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99% of the compound of the composition in one of the salt or crystalline forms. In some embodiments, essentially 100% of the Compound 1 of an API formulation is in a salt or crystalline form as described herein.

Any of the crystalline forms of Compound 1, including salts and solvated forms, can be useful as an active pharmaceutical ingredient (API) for preparation of pharmaceutical compositions. However, solvent-free forms are generally preferred for this purpose. A hydrate is considered solvent-free for this purpose. Solvated forms can be, as indicated above, useful as process intermediates in preparation of solvent-free forms. Compound 1 salts and crystalline forms can be used in preparation of pharmaceutical compositions suitable for various routes of administration, including oral, to a subject in need thereof. Thus, in some embodiments, a pharmaceutical composition is provided, comprising a crystalline form of Compound 1 and one or more pharmaceutically acceptable excipients. Such compositions can be prepared using various known processes of pharmacy.

In some embodiments, the salt or crystalline form of Compound 1 includes those of Compound 1 free base anhydrate having PXRD pattern A, Compound 1 free base anhydrate having PXRD pattern B, Compound 1 free base hydrate having PXRD pattern C, Compound 1 free base hydrate having PXRD pattern D, Compound 1 free base dichloromethane solvate having pattern E, Compound 1 free base ethyl acetate solvate having PXRD pattern F, Compound 1 free base ethyl acetate solvate having PXRD pattern G, Compound 1 free base acetonitrile solvate having PXRD pattern H, Compound 1 free base acetonitrile solvate having PXRD pattern I, Compound 1 free base acetone solvate having PXRD pattern J, Compound 1 hydrochloride having PXRD pattern K, Compound 1 hydrochloride hydrate having PXRD pattern L, Compound 1 sulfate having PXRD pattern M, and Compound 1 free base tetrahydrofuran (THF) solvate having PXRD pattern N, each having the respective powder X-ray diffraction patterns as described herein.

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According to any of these embodiments, the composition can be deliverable, for example, by the oral route. Other routes of administration include without limitation parenteral, sublingual, buccal, intranasal, pulmonary, topical, transdermal, intradermal, ocular, otic, rectal, vaginal, intra-gastric, intracranial, intrasynovial and intra-articular routes.

Where it is desired to provide Compound 1 free base or salt in solution form, for example in a liquid formulation for oral or parenteral administration, the Compound 1 free base or salt will not, of course, be present in such a formulation in crystalline form; indeed, the presence of crystals is generally undesired in such a formulation. However, a crystalline form of Compound 1 free base can nonetheless be important as API in a process for preparing such a formulation. Thus, the present disclosure further provides a process for preparing a pharmaceutical solution composition of Compound 1 comprising dissolving a crystalline salt or a crystalline form of Compound 1 free base in a pharmaceutically acceptable solvent or mixture of solvents. Even where the desired formulation is one containing Compound 1 free base in amorphous form, for example a solid melt formulation, a crystalline form of Compound 1 free base can still be useful as API in a process for preparing such a formulation.

As API, a crystalline form of Compound 1 free base or mixtures thereof can have advantages over an amorphous form. For example, purification of API to the high degree of purity required by most regulatory authorities can be more efficient and therefore cost less where the API is in crystalline form as opposed to amorphous form. Physical and chemical stability, and therefore shelf-life of the API solid, can also be better for crystalline than amorphous forms. Ease of handling can be improved over the amorphous form, which can be oily or sticky. Drying can be more straightforward and more easily controlled in the case of the crystalline material, which can have a well-defined drying or desolvation temperature, than in the case of the amorphous material, which can have greater affinity for organic solvents and no well-defined drying temperature. Downstream processing using crystalline API can further permit enhanced process control. In preparing a liquid formulation, for example a solution in a lipid carrier, crystalline Compound 1 can dissolve faster and can have a reduced tendency to form a gel during dissolution. These advantages are illustrative and non-limiting.

Pharmaceutical compositions comprising crystalline Compound 1 free base, or prepared using crystalline Compound 1 free base or salts of Compound 1 as API, contain Compound 1 in an amount that can be therapeutically effective when the composition is administered to a subject in need thereof according to an appropriate regimen. Dosage amounts are expressed herein as free base equivalent amounts unless the context requires otherwise. Typically, a unit dose (the amount administered at a single time), which can be administered at an appropriate frequency, e.g., twice daily to once weekly, is about 10 to about 1,000 mg. Where frequency of administration is once daily (q.d.), unit dose and daily dose are the same. Illustratively, the unit dose of Compound 1 in a composition of the invention can be about 25 to about 1,000 mg, more typically about 50 to about 500 mg, for example about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450 or about 500 mg. Where the composition is prepared as a discrete dosage form such as a tablet or capsule, a unit dose can be deliverable in a single dosage form or a small plurality of dosage forms, most typically 1 to about 10 dosage forms.

The higher the unit dose, the more desirable it becomes to select excipients that permit a relatively high loading of API (in this case Compound 1 free base or salt) in the formulation.

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Typically, the concentration of Compound 1 in a formulation prepared according to the present disclosure is at least about 1%, e.g., about 1% to about 25%, by weight, but lower and higher concentrations can be acceptable or achievable in specific cases. Illustratively, the Compound 1 free base equivalent concentration in various embodiments is at least about 2%, e.g., about 2% to about 20%, by weight, for example about 5%, about 10% or about 15%, by weight of the formulation.

A composition prepared according to the invention comprises, in addition to the API, one or more pharmaceutically acceptable excipients. If the composition is to be prepared in solid form for oral administration, for example as a tablet or capsule, it typically includes at least one or more solid diluents and one or more solid disintegrants. Optionally, the excipients further include one or more binding agents, wetting agents and/or antifrictional agents (lubricants, anti-adherents and/or glidants). Many excipients have two or more functions in a pharmaceutical composition. Characterization herein of a particular excipient as having a certain function, e.g., diluent, disintegrant, binding agent, etc., should not be read as limiting to that function. Further information on excipients can be found in standard reference works such as *Handbook of Pharmaceutical Excipients*, 3rd ed. (Kibbe, ed. (2000), Washington: American Pharmaceutical Association).

Suitable diluents illustratively include, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; lactitol; maltitol; mannitol; sorbitol; xylitol; dextrose and dextrose monohydrate; fructose; sucrose and sucrose-based diluents such as compressible sugar, confectioner's sugar and sugar spheres; maltose; inositol; hydrolyzed cereal solids; starches (e.g., corn starch, wheat starch, rice starch, potato starch, tapioca starch, etc.), starch components such as amylose and dextrates, and modified or processed starches such as pregelatinized starch; dextrans; celluloses including powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, food grade sources of  $\alpha$ - and amorphous cellulose and powdered cellulose, and cellulose acetate; calcium salts including calcium carbonate, tribasic calcium phosphate, dibasic calcium phosphate dihydrate, monobasic calcium sulfate monohydrate, calcium sulfate and granular calcium lactate trihydrate; magnesium carbonate; magnesium oxide; bentonite; kaolin; sodium chloride; and the like. Such diluents, if present, typically constitute in total about 5% to about 95%, for example about 20% to about 90%, or about 50% to about 85%, by weight of the composition. The diluent or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Microcrystalline cellulose and silicified microcrystalline cellulose are particularly useful diluents, and are optionally used in combination with a water-soluble diluent such as mannitol. Illustratively, a suitable weight ratio of microcrystalline cellulose or silicified microcrystalline cellulose to mannitol is about 10:1 to about 1:1, but ratios outside this range can be useful in particular circumstances.

Suitable disintegrants include, either individually or in combination, starches including pregelatinized starch and sodium starch glycolate; clays; magnesium aluminum silicate; cellulose-based disintegrants such as powdered cellulose, microcrystalline cellulose, methylcellulose, low-substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium and croscarmellose sodium; alginates; povidone; crospovidone; polacrillin potassium; gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums; colloidal silicon dioxide; and the like. One or more disintegrants, if present, typically constitute in total



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about 0.2% to about 30%, for example about 0.5% to about 20%, or about 1% to about 10%, by weight of the composition.

Sodium starch glycolate is a particularly useful disintegrant, and typically constitutes in total about 1% to about 20%, for example about 2% to about 15%, or about 5% to about 10%, by weight of the composition.

Binding agents or adhesives are useful excipients, particularly where the composition is in the form of a tablet. Such binding agents and adhesives should impart sufficient cohesion to the blend being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Suitable binding agents and adhesives include, either individually or in combination, acacia; tragacanth; glucose; polydextrose; starch including pregelatinized starch; gelatin; modified celluloses including methylcellulose, carmellose sodium, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, hydroxyethylcellulose and ethylcellulose; dextrans including maltodextrin; zein; alginic acid and salts of alginic acid, for example sodium alginate; magnesium aluminum silicate; bentonite; polyethylene glycol (PEG); polyethylene oxide; guar gum; polysaccharide acids; polyvinylpyrrolidone (povidone or PVP), for example povidone K-15, K-30 and K-29/32; polyacrylic acids (carbomers); polymethacrylates; and the like. One or more binding agents and/or adhesives, if present, typically constitute in total about 0.5% to about 25%, for example about 1% to about 15%, or about 1.5% to about 10%, by weight of the composition.

Povidone and hydroxypropylcellulose, either individually or in combination, are particularly useful binding agents for tablet formulations, and, if present, typically constitute about 0.5% to about 15%, for example about 1% to about 10%, or about 2% to about 8%, by weight of the composition.

Wetting agents, if present, are normally selected to maintain the drug in close association with water, a condition that can improve bioavailability of the composition. Non-limiting examples of surfactants that can be used as wetting agents include, either individually or in combination, quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride; dioctyl sodium sulfosuccinate; polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10 and octoxynol 9; poloxamers (polyoxyethylene and polyoxypropylene block copolymers); polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides, polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example ceteth-10, laureth-4, laureth-23, oleth-2, oleth-10, oleth-20, steareth-2, steareth-10, steareth-20, steareth-100 and polyoxyethylene (20) cetostearyl ether; polyoxyethylene fatty acid esters, for example polyoxyethylene (20) stearate, polyoxyethylene (40) stearate and polyoxyethylene (100) stearate; sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate; polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80; propylene glycol fatty acid esters, for example propylene glycol laurate; sodium lauryl sulfate; fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate; glyceryl fatty acid esters, for example glyceryl monooleate, glyceryl monostearate and glyceryl palmitostearate; tyloxapol; and the like. One or more wetting agents, if present, typically constitute in total about 0.1% to about 15%, for example about 0.2% to about 10%, or about 0.5% to about 7%, by weight of the composition.

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Nonionic surfactants, more particularly poloxamers, are examples of wetting agents that can be useful herein. Illustratively, a poloxamer such as Pluronic™ F127, if present, can constitute about 0.1% to about 10%, for example about 0.2% to about 7%, or about 0.5% to about 5%, by weight of the composition.

Lubricants reduce friction between a tableting mixture and tableting equipment during compression of tablet formulations. Suitable lubricants include, either individually or in combination, glyceryl behenate; stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils; glyceryl palmitostearate; talc; waxes; sodium benzoate; sodium acetate; sodium fumarate; sodium stearyl fumarate; PEGs (e.g., PEG 4000 and PEG 6000); poloxamers; polyvinyl alcohol; sodium oleate; sodium lauryl sulfate; magnesium lauryl sulfate; and the like. One or more lubricants, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 5%, or about 0.2% to about 2%, by weight of the composition. Sodium stearyl fumarate is a particularly useful lubricant.

Anti-adherents reduce sticking of a tablet formulation to equipment surfaces. Suitable anti-adherents include, either individually or in combination, talc, colloidal silicon dioxide, starch, DL-leucine, sodium lauryl sulfate and metallic stearates. One or more anti-adherents, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 7%, or about 0.2% to about 5%, by weight of the composition. Colloidal silicon dioxide is a particularly useful anti-adherent.

Glidants improve flow properties and reduce static in a tableting mixture. Suitable glidants include, either individually or in combination, colloidal silicon dioxide, starch, powdered cellulose, sodium lauryl sulfate, magnesium trisilicate and metallic stearates. One or more glidants, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 7%, or about 0.2% to about 5%, by weight of the composition. Colloidal silicon dioxide is a particularly useful glidant.

Other excipients such as buffering agents, stabilizers, antioxidants, antimicrobials, colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in compositions of the present invention. Tablets can be uncoated or can comprise a core that is coated, for example with a non-functional film or a release-modifying or enteric coating. Capsules can have hard or soft shells comprising, for example, gelatin (in the form of hard gelatin capsules or soft elastic gelatin capsules), starch, carrageenan and/or HPMC, optionally together with one or more plasticizers.

A solid orally deliverable composition of the present invention is not limited by any process used to prepare it. Any suitable process of pharmacy can be used, including dry blending with or without direct compression, and wet or dry granulation.

If the composition is to be prepared in liquid (including encapsulated liquid) form, the API (e.g., crystalline Compound 1 free base or salt) can be, for example, dissolved in a suitable carrier, typically one comprising a lipid solvent for the API. The higher the unit dose, the more desirable it becomes to select a carrier that permits a relatively high concentration of the drug in solution therein. Typically, the free base equivalent concentration of API in the carrier is at least about 10 mg/ml, e.g., about 10 to about 500 mg/ml, but lower and higher concentrations can be acceptable or achievable in specific cases. Illustratively, the drug concentration in various embodiments is at least about 10 mg/ml, e.g., about 10 to about 250 mg/ml, or at least about 20 mg/ml, e.g., about

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20 to about 200 mg/ml, for example about 20, about 25, about 30, about 40, about 50, about 75, about 100 or about 150 mg/ml.

The carrier can be substantially non-aqueous, i.e., having no water, or having an amount of water that is small enough to be, in practical terms, essentially non-deleterious to performance or properties of the composition. Typically, the carrier comprises zero to less than about 5% by weight water. It will be understood that certain ingredients useful herein can bind small amounts of water on or within their molecules or supramolecular structures; such bound water if present does not affect the "substantially non-aqueous" character of a carrier as defined herein.

In some embodiments, the carrier comprises one or more glyceride materials. Suitable glyceride materials include, without limitation, medium to long chain mono-, di- and triglycerides. The term "medium chain" herein refers to hydrocarbyl chains individually having no less than about 6 and less than about 12 carbon atoms, including for example C<sub>8</sub> to C<sub>10</sub> chains. Thus glyceride materials comprising caprylyl and capryl chains, e.g., caprylic/capric mono-, di- and/or triglycerides, are examples of "medium chain" glyceride materials herein. The term "long chain" herein refers to hydrocarbyl chains individually having at least about 12, for example about 12 to about 18, carbon atoms, including for example lauryl, myristyl, cetyl, stearyl, oleyl, linoleyl and linolenyl chains. Medium to long chain hydrocarbyl groups in the glyceride materials can be saturated, mono- or polyunsaturated.

In one embodiment the carrier comprises a medium chain and/or a long chain triglyceride material. A suitable example of a medium chain triglyceride material is a caprylic/capric triglyceride product such as, for example, Captex 355 EPTM of Abitec Corp. and products substantially equivalent thereto. Suitable examples of long chain triglycerides include any pharmaceutically acceptable vegetable oil, for example canola, coconut, corn, cottonseed, flaxseed, olive, palm, peanut, safflower, sesame, soy and sunflower oils, and mixtures of such oils. Oils of animal, particularly marine animal, origin can also be used, including for example fish oil.

In some embodiments the carrier comprises a phospholipid and a pharmaceutically acceptable solubilizing agent for the phospholipid. It will be understood that reference in the singular to a (or the) phospholipid, solubilizing agent or other formulation ingredient herein includes the plural; thus combinations, for example mixtures, of more than one phospholipid, or more than one solubilizing agent, are expressly contemplated herein. The solubilizing agent, or the combination of solubilizing agent and phospholipid, also solubilizes the drug, although other carrier ingredients, such as a surfactant or an alcohol such as ethanol, optionally present in the carrier can in some circumstances provide enhanced solubilization of the drug.

Any pharmaceutically acceptable phospholipid or mixture of phospholipids can be used. In general such phospholipids are phosphoric acid esters that yield on hydrolysis phosphoric acid, fatty acid(s), an alcohol and a nitrogenous base. Pharmaceutically acceptable phospholipids can include without limitation phosphatidylcholines, phosphatidylserines and phosphatidylethanolamines. In one embodiment the composition comprises phosphatidylcholine, derived for example from natural lecithin. Any source of lecithin can be used, including animal sources such as egg yolk, but plant sources are generally preferred. Soy is a particularly rich source of lecithin that can provide phosphatidylcholine for use in the present invention.

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Illustratively, a suitable amount of phospholipid is about 15% to about 75%, for example about 30% to about 60%, by weight of the carrier, although greater and lesser amounts can be useful in particular situations.

Ingredients useful as components of the solubilizing agent are not particularly limited and will depend to some extent on the desired concentration of drug and of phospholipid. In one embodiment, the solubilizing agent comprises one or more glycols and/or one or more glyceride materials.

Suitable glycols include propylene glycol and polyethylene glycols (PEGs) having molecular weight of about 200 to about 1,000 g/mol, e.g., PEG-400, which has an average molecular weight of about 400 g/mol. Such glycols can provide relatively high solubility of the drug; however the potential for oxidative degradation of the drug can be increased when in solution in a carrier comprising such glycols, for example because of the tendency of glycols to produce superoxides, peroxides and/or free hydroxyl radicals. The higher the glycol content of the carrier, the greater may be the tendency for degradation of a chemically unstable drug. In one embodiment, therefore, one or more glycols are present in a total glycol amount of at least about 1% but less than about 50%, for example less than about 30%, less than about 20%, less than about 15% or less than about 10% by weight of the carrier. In another embodiment, the carrier comprises substantially no glycol.

Suitable glyceride materials for use together with a phospholipid include, without limitation, those mentioned above. Where one or more glyceride materials are present as a major component of the solubilizing agent, a suitable total amount of glycerides is an amount effective to solubilize the phospholipid and, in combination with other components of the carrier, effective to maintain the drug and antioxidant in solution. For example, glyceride materials such as medium chain and/or long chain triglycerides can be present in a total glyceride amount of about 5% to about 70%, for example about 15% to about 60% or about 25% to about 50%, by weight of the carrier.

Additional solubilizing agents that are other than glycols or glyceride materials can be included if desired. Such agents, for example N-substituted amide solvents such as dimethylformamide (DMF) and N,N-dimethylacetamide (DMA), can, in specific cases, assist in raising the limit of solubility of the drug in the carrier, thereby permitting increased drug loading. However, N-substituted amides including DMF and DMA can present regulatory and/or toxicological issues that restrict the amount of such solvents that can be used in a formulation. Furthermore, the carriers useful herein generally provide adequate solubility of small-molecule drugs of interest herein without such additional agents.

Even when a sufficient amount of a glycol or glyceride material is present to solubilize the phospholipid, the resulting carrier solution and/or the drug-carrier system may be rather viscous and difficult or inconvenient to handle. In such cases it may be found desirable to include in the carrier a viscosity reducing agent in an amount effective to provide acceptably low viscosity. An example of such an agent is an alcohol, more particularly ethanol, which is preferably introduced in a form that is substantially free of water, for example 99% ethanol, dehydrated alcohol USP or absolute ethanol. Excessively high concentrations of ethanol should, however, generally be avoided. This is particularly true where, for example, the drug-carrier system is to be administered in a gelatin capsule, because of the tendency of high ethanol concentrations to result in mechanical failure of the capsule. In

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general, suitable amounts of ethanol are 0% to about 25%, for example about 1% to about 20% or about 3% to about 15%, by weight of the carrier.

Optionally, the carrier further comprises a pharmaceutically acceptable non-phospholipid surfactant. One of skill in the art will be able to select a suitable surfactant for use in a composition of the invention. Illustratively, a surfactant such as polysorbate 80 can be included in an amount of 0% to about 5%, for example 0% to about 2% or 0% to about 1%, by weight of the carrier.

Conveniently, pre-blended products are available containing a suitable phospholipid+solubilizing agent combination for use in compositions of the present invention. Pre-blended phospholipid+solubilizing agent products can be advantageous in improving ease of preparation of the present compositions.

An illustrative example of a pre-blended phospholipid+solubilizing agent product is Phosal 50 PG<sup>TM</sup>, available from Phospholipid GmbH, Germany, which comprises, by weight, not less than 50% phosphatidylcholine, not more than 6% lysophosphatidylcholine, about 35% propylene glycol, about 3% mono- and diglycerides from sunflower oil, about 2% soy fatty acids, about 2% ethanol, and about 0.2% ascorbyl palmitate.

Another illustrative example is Phosal 53 MCT<sup>TM</sup>, also available from Phospholipid GmbH, which contains, by weight, not less than 53% phosphatidylcholine, not more than 6% lysophosphatidylcholine, about 29% medium chain triglycerides, 3-6% (typically about 5%) ethanol, about 3% mono- and diglycerides from sunflower oil, about 2% oleic acid, and about 0.2% ascorbyl palmitate (reference composition). A product having the above or substantially equivalent composition, whether sold under the Phosal 53 MCT<sup>TM</sup> brand or otherwise, is generically referred to herein as "phosphatidylcholine+medium chain triglycerides 53/29". A product having "substantially equivalent composition" in the present context means having a composition sufficiently similar to the reference composition in its ingredient list and relative amounts of ingredients to exhibit no practical difference in properties with respect to utilization of the product herein.

Yet another illustrative example is Phosal 50 SA<sup>TM</sup>, also available from Phospholipid GmbH, which contains, by weight, not less than 50% phosphatidylcholine and not more than 6% lysophosphatidylcholine in a solubilizing system comprising safflower oil and other ingredients.

The phosphatidylcholine component of each of these pre-blended products can be derived from soy lecithin. Products of substantially equivalent composition may be obtainable from other suppliers.

A pre-blended product such as Phosal 50 PG<sup>TM</sup>, Phosal 53 MCT<sup>TM</sup> or Phosal 50 SA<sup>TM</sup> can, in some embodiments, constitute substantially the entire carrier system. In other embodiments, additional ingredients are present, for example ethanol (additional to any that may be present in the pre-blended product), non-phospholipid surfactant such as polysorbate 80, polyethylene glycol and/or other ingredients. Such additional ingredients, if present, are typically included in only minor amounts. Illustratively, phosphatidylcholine+medium chain triglycerides 53/29 can be included in the carrier in an amount of about 50% to 100%, for example about 80% to 100%, by weight of the carrier.

Without being bound by theory, it is believed that the therapeutic efficacy of Compound 1 is due at least in part to its ability to bind to a Bcl-2 family protein such as Bcl-2, Bcl-X<sub>L</sub> or Bcl-w in a way that inhibits the anti-apoptotic action of the protein, for example by occupying the BH3 binding groove of the protein.

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In still further embodiments of the invention, there is provided a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising administering to a subject having the disease a therapeutically effective amount of crystalline Compound 1 free base or a pharmaceutical composition comprising a salt or crystalline form of Compound 1 free base and one or more pharmaceutically acceptable excipients.

In still further embodiments of the invention, there is provided a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein is provided, where the method comprises preparing a solution or dispersion of a salt or crystalline form of Compound 1 described herein in a pharmaceutically acceptable solvent or mixture of solvents, and administering the resulting solution or dispersion in a therapeutically effective amount to a subject having the disease.

The subject can be human or non-human (e.g., a farm, zoo, work or companion animal, or a laboratory animal used as a model) but in an important embodiment the subject is a human patient in need of the drug, for example to treat a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein. A human subject can be male or female and of any age, but is typically an adult.

The composition is normally administered in an amount providing a therapeutically effective daily dose of the drug. The term "daily dose" herein means the amount of drug administered per day, regardless of the frequency of administration. For example, if the subject receives a unit dose of 150 mg twice daily, the daily dose is 300 mg. Use of the term "daily dose" will be understood not to imply that the specified dosage amount is necessarily administered once daily. However, in a particular embodiment the dosing frequency is once daily (q.d.), and the daily dose and unit dose are in this embodiment the same thing.

What constitutes a therapeutically effective dose depends on the bioavailability of the particular formulation, the subject (including species and body weight of the subject), the disease (e.g., the particular type of cancer) to be treated, the stage and/or severity of the disease, the individual subject's tolerance of the compound, whether the compound is administered in monotherapy or in combination with one or more other drugs, e.g., other chemotherapeutics for treatment of cancer, and other factors. Thus, the daily dose can vary within wide margins, for example from about 10 to about 1,000 mg. Greater or lesser daily doses can be appropriate in specific situations. It will be understood that recitation herein of a "therapeutically effective" dose herein does not necessarily require that the drug be therapeutically effective if only a single such dose is administered; typically therapeutic efficacy depends on the composition being administered repeatedly according to a regimen involving appropriate frequency and duration of administration. It is strongly preferred that, while the daily dose selected is sufficient to provide benefit in terms of treating the cancer, it should not be sufficient to provoke an adverse side-effect to an unacceptable or intolerable degree. A suitable therapeutically effective dose can be selected by the physician of ordinary skill without undue experimentation based on the disclosure herein and on art cited herein, taking into account factors such as those mentioned above. The physician may, for example, start a cancer patient on a course of therapy with a relatively low daily dose and titrate the dose upwards over a period of days or weeks, to reduce risk of adverse side-effects.

Illustratively, suitable doses of Compound 1 are generally about 25 to about 1000 mg/day or about 50 to about 1000



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mg/day, more typically about 50 to about 500 mg/day or about 200 to about 400 mg/day, for example about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 750 or about 1000 mg/day, administered at an average dosage interval of about 3 hours to about 7 days, for example about 8 hours to about 3 days, or about 12 hours to about 2 days. In most cases a once-daily (q.d.) administration regimen is suitable.

In certain embodiments, the invention relates to a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising administering to a subject having the disease a therapeutically effective amount of (a) Compound 1 in a salt or crystalline form or (b) a pharmaceutical composition comprising Compound 1 in a salt or crystalline form and one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount is administered orally in a dose of about 50 to about 1000 mg Compound 1 per day at an average treatment interval of about 3 hours to about 7 days.

In certain embodiments, the invention relates to a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising administering to a subject having the disease a therapeutically effective amount of (a) Compound 1 in a salt or crystalline form or (b) a pharmaceutical composition comprising Compound 1 in a salt or crystalline form and one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount is administered orally once daily in a dose of about 200 to about 400 mg Compound 1 free base equivalent per day.

In certain embodiments, the invention relates to a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising administering a solution or dispersion of Compound 1 in a salt or crystalline form to a subject having the disease, wherein the solution is administered orally in a dose of about 50 to about 1000 mg Compound 1 per day at an average treatment interval of about 3 hours to about 7 days.

In certain embodiments, the invention relates to a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising administering a solution or dispersion of Compound 1 in a salt or crystalline form to a subject having the disease, wherein the solution is administered orally once daily in a dose of about 200 to about 400 mg Compound 1 free base equivalent per day.

An "average dosage interval" herein is defined as a span of time, for example one day or one week, divided by the number of unit doses administered over that span of time. For example, where a drug is administered three times a day, around 8 am, around noon and around 6 pm, the average dosage interval is 8 hours (a 24-hour time span divided by 3). If the drug is formulated as a discrete dosage form such as a tablet or capsule, a plurality (e.g., 2 to about 10) of dosage forms administered at one time is considered a unit dose for the purpose of defining the average dosage interval.

Compositions prepared according to the present invention are suitable for use in monotherapy or in combination therapy, for example with other chemotherapeutics or with ionizing radiation. A particular advantage of the present invention is that it permits once-daily oral administration, a regimen which is convenient for the patient who is undergoing treatment with other orally administered drugs on a once-daily regimen. Oral administration is easily accomplished by the patient him/herself or by a caregiver in the patient's home; it is also a convenient route of administration for patients in a hospital or residential care setting.

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Combination therapies illustratively include administration of a composition comprising (or prepared using as API) one or more crystalline forms of Compound 1 (including crystalline salt forms) concomitantly with one or more of bortezomid, carboplatin, cisplatin, cyclophosphamide, dacarbazine, dexamethasone, docetaxel, doxorubicin, etoposide, fludarabine, hydroxydoxorubicin, irinotecan, paclitaxel, rapamycin, rituximab, vincristine and the like, for example with a polytherapy such as CHOP (cyclophosphamide+hydroxydoxorubicin+vincristine+prednisone), RCVP (rituximab+cyclophosphamide+vincristine+prednisone), R-CHOP (rituximab+CHOP) or DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab).

A Compound 1 composition can be administered in combination therapy with one or more therapeutic agents that include, but are not limited to, angiogenesis inhibitors, anti-proliferative agents, other apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1 inhibitors), activators of a death receptor pathway, BiTE (bi-specific T-cell engager) antibodies, dual variable domain binding proteins (DVDs), inhibitors of apoptosis proteins (IAPs), microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, poly-ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, small inhibitory ribonucleic acids (siRNAs), kinase inhibitors, receptor tyrosine kinase inhibitors, aurora kinase inhibitors, polo-like kinase inhibitors, bcr-abl kinase inhibitors, growth factor inhibitors, COX-2 inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), antimitotic agents, alkylating agents, antimetabolites, intercalating antibiotics, platinum-containing chemotherapeutic agents, growth factor inhibitors, ionizing radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biologic response modifiers, immunologicals, antibodies, hormonal therapies, retinoids, deltidoids, plant alkaloids, proteasome inhibitors, HSP-90 inhibitors, histone deacetylase (HDAC) inhibitors, purine analogs, pyrimidine analogs, MEK inhibitors, CDK inhibitors, ErbB2 receptor inhibitors, mTOR inhibitors as well as other antitumor agents.

Angiogenesis inhibitors include, but are not limited to, EGFR inhibitors, PDGFR inhibitors, VEGFR inhibitors, TIE2 inhibitors, IGF1R inhibitors, matrix metalloproteinase 2 (MMP-2) inhibitors, matrix metalloproteinase 9 (MMP-9) inhibitors and thrombospondin analogs.

Examples of EGFR inhibitors include, but are not limited to, gefitinib, erlotinib, cetuximab, EMD-7200, ABX-EGF, HR3, IgA antibodies, TP-38 (IVAX), EGFR fusion protein, EGF-vaccine, anti-EGFR immunoliposomes and lapatinib.

Examples of PDGFR inhibitors include, but are not limited to, CP-673451 and CP-868596.

Examples of VEGFR inhibitors include, but are not limited to, bevacizumab, sunitinib, sorafenib, CP-547632, axitinib, vandetanib, AEE788, AZD-2171, VEGF trap, vatalanib, pegaptanib, IM862, pazopanib, ABT-869 and angiozyme.

Bcl-2 family protein inhibitors other than Compound 1 include, but are not limited to, ABT-263, AT-101 ((-)-gossypol), Genasense™ Bcl-2-targeting antisense oligonucleotide (G3139 or oblimersen), IPI-194, IPI-565, N-(4-(4-(4-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide (ABT-737), GX-070 (obatoclax) and the like.

Activators of a death receptor pathway include, but are not limited to, TRAIL, antibodies or other agents that target death receptors (e.g., DR4 and DR5) such as apomab, conatumumab, ETR2-ST01, GDC0145 (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.



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Examples of thrombospondin analogs include, but are not limited to, TSP-1, ABT-510, ABT-567 and ABT-898.

Examples of aurora kinase inhibitors include, but are not limited to, VX-680, AZD-1152 and MLN-8054.

An example of a polo-like kinase inhibitor includes, but is not limited to, BI-2536.

Examples of bcr-abl kinase inhibitors include, but are not limited to, imatinib and dasatinib.

Examples of platinum-containing agents include, but are not limited to, cisplatin, carboplatin, eptaplatin, lobaplatin, nedaplatin, oxaliplatin and satraplatin.

Examples of mTOR inhibitors include, but are not limited to, CCI-779, rapamycin, temsirolimus, everolimus, RAD001 and AP-23573.

Examples of HSP-90 inhibitors include, but are not limited to, geldanamycin, radicicol, 17-AAG, KOS-953, 17-DMAG, CNF-101, CNF-1010, 17-AAG-nab, NCS-683664, efungumab, CNF-2024, PU3, PU24FC1, VER-49009, IPI-504, SNX-2112 and STA-9090.

Examples of HDAC inhibitors include, but are not limited to, suberoylanilide hydroxamic acid (SAHA), MS-275, valproic acid, TSA, LAQ-824, trapoxin and depsipeptide.

Examples of MEK inhibitors include, but are not limited to, PD-325901, ARRY-142886, ARRY-438162 and PD-98059.

Examples of CDK inhibitors include, but are not limited to, flavopyridol, MCS-5A, CVT-2584, seliciclib ZK-304709, PHA-690509, BMI-1040, GPC-286199, BMS-387032, PD-332991 and AZD-5438.

Examples of COX-2 inhibitors include, but are not limited to, celecoxib, parecoxib, deracoxib, ABT-963, etoricoxib, lumiracoxib, BMS-347070, RS 57067, NS-398, valdecoxib, rofecoxib, SD-8381, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoyl-phenyl)-1H-pyrrole, T-614, JTE-522, S-2474, VIT-2016, CT-3 and SC-58125.

Examples of NSAIDs include, but are not limited to, salicylate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac and oxaprozin.

Examples of ErbB2 receptor inhibitors include, but are not limited to, CP-724714, canertinib, trastuzumab, pertuzumab, TAK-165, ionafamib, GW-282974, EKB-569, PI-166, dHER2, APC-8024, anti-HER/2neu bispecific antibody B7.her2IgG3 and HER2 trifunctional bispecific antibodies mAB AR-209 and mAB 2B-1.

Examples of alkylating agents include, but are not limited to, nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, Cloretazine™ (laromustine), AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, carmustine, estramustine, fotemustine, glufosfamide, KW-2170, mafosfamide, mitolactol, lomustine, treosulfan, dacarbazine and temozolomide.

Examples of antimetabolites include, but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, tegafur, UFT, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, pemetrexed, gemcitabine, fludarabine, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethenylcytidine, cytosine arabinoside, hydroxyurea, TS-1, melphalan, nelarabine, nolatrexed, disodium pemetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, mycophenolic acid, ocfosfate, pentostatin, tiazofurin, ribavirin, EICAR, hydroxyurea and deferoxamine.

Examples of antibiotics include, but are not limited to, intercalating antibiotics, aclarubicin, actinomycin D, amru-

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bicin, annamycin, adriamycin, bleomycin, daunorubicin, doxorubicin (including liposomal doxorubicin), elsamitrucin, epirubicin, glarubicin, idarubicin, mitomycin C, nemo-rubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin, zinostatin and combinations thereof.

Examples of topoisomerase inhibiting agents include, but are not limited to, aclarubicin, amonafide, belotecan, camptothecin, 10-hydroxycamptothecin, 9-amino-camptothecin, amsacrine, dexrazoxane, diflomotecan, irinotecan HCl, edotecarin, epirubicin, etoposide, exatecan, becatecarin, gimatecan, lurtotecan, orathecin, BN-80915, mitoxantrone, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide and topotecan.

Examples of antibodies include, but are not limited to, rituximab, cetuximab, bevacizumab, trastuzumab, CD40-specific antibodies and IGF1R-specific antibodies, chTNT-1/B, denosumab, edrecolomab, WX G250, zanolimumab, linituzumab and ticilimumab.

Examples of hormonal therapies include, but are not limited to, sevelamer carbonate, rilostane, luteinizing hormone releasing hormone, modrastane, exemestane, leuprolide acetate, buserelin, cetorelix, deslorelin, histrelin, anastrozole, fosreltin, goserelin, degarelix, doxercalciferol, fadrozole, formestane, tamoxifen, arzoxifen, bicalutamide, abarelix, triptorelin, finasteride, fulvestrant, toremifene, raloxifene, trilostane, lasofoxifene, letrozole, flutamide, megestrol, mifepristone, nilutamide, dexamethasone, prednisone and other glucocorticoids.

Examples of retinoids or deltoids include, but are not limited to, seocalcitol, lexacalcitol, fenretinide, aliretinoin, tretinoin, bexarotene and LGD-1550.

Examples of plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine and vinorelbine.

Examples of proteasome inhibitors include, but are not limited to, bortezomib, MG-132, NPI-0052 and PR-171.

Examples of immunologicals include, but are not limited to, interferons and numerous other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, interferon gamma-1b, interferon gamma-n1 and combinations thereof. Other agents include filgrastim, lentinan, sizofilan, BCG live, ubenimex, WF-10 (tetrachlorodecaoxide or TCDO), aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab ozogamicin, ibritumomab, imiquimod, lenograstim, melanoma vaccine, molgramostim, sargaramostim, tasonermin, teceleukin, thymalasin, tositumomab, Virulizin™ immunotherapeutic of Lorus Pharmaceuticals, Z-100 (specific substance of Maruyama or SSM), Zevalin™ (90Y-ibritumomab tiuxetan), epratuzumab, mitumomab, oregovomab, pemtumorab, Provenge™ (sipuleucel-T), teceleukin, Therocys™ (Bacillus Calmette-Guerin), cytotoxic lymphocyte antigen 4 (CTLA4) antibodies and agents capable of blocking CTLA4 such as MDX-010.

Examples of biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity. Such agents include, but are not limited to, krestin, lentinan, sizofuran, picibanil, PF-3512676 and ubenimex.

Examples of pyrimidine analogs include, but are not limited to, 5-fluorouracil, floxuridine, doxifluridine, raltitrexed, cytarabine, cytosine arabinoside, fludarabine, triacetyldine, troxacitabine and gemcitabine.

Examples of purine analogs include, but are not limited to, mercaptopurine and thioguanine.

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Examples of antimitotic agents include, but are not limited to, N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, paclitaxel, docetaxel, larotaxel, epothilone D, PNU-100940, batabulin, ixabepilone, patupilone, XRP-9881, vinflunine and ZK-EPO (synthetic epothilone).

Examples of radiotherapy include, but are not limited to, external beam radiotherapy (XBRT), teletherapy, brachytherapy, sealed-source radiotherapy and unsealed-source radiotherapy.

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include, but are not limited to, adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (Sutton et al. (1997) *J. Immunol.* 158:5783-5790).

siRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxy-nucleotide, 2'-OCH<sub>3</sub>-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/or the 3'-ends of a given strand. For example, siRNAs targeting Mcl-1 have been shown to enhance the activity of the apoptosis-promoting agent ABT-263 (Tse et al. (2008) *Cancer Res.* 68:3421-3428 and references therein).

Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy-chain DVD polypeptides and two light-chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy-chain DVD polypeptide, a light-chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy-chain variable domain and a light-chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

PARP inhibitors include, but are not limited to, ABT-888, olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

Additionally or alternatively, a composition of the present invention can be administered in combination therapy with

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one or more antitumor agents selected from ABT-100, N-acetylcolchicol-O-phosphate, acitretin, AE-941, aglycon protopanaxadiol, arglabin, arsenic trioxide, AS04 adjuvant-adsorbed HPV vaccine, L-asparaginase, atamestane, atrasentan, AVE-8062, bosentan, canfosfamide, Canvaxin™, catumaxomab, CeaVac™ celmoleukin, combrestatin A4P, contusogene ladenovec, Cotara™, cyproterone, deoxycoformycin, dexrazoxane, N,N-diethyl-2-(4-(phenylmethyl)phenoxy)ethanamine, 5,6-dimethylxanthenone-4-acetic acid, docosahexaenoic acid/paclitaxel, discodermolide, efaproxiral, enzastaurin, epothilone B, ethynyluracil, exisulind, falimarev, Gastrimmune™ GMK vaccine, GVAX™, halofuginone, histamine, hydroxycarbamide, ibandronic acid, ibritumomab tiuxetan, IL-13-PE38, inalimarev, interleukin 4, KSB-311, lanreotide, lenalidomide, lonafarnib, lovastatin, 5,10-methylenetetrahydrofolate, mifamurtide, miltefosine, motexafin, oblimersen, OncoVAX™, Osidem™, paclitaxel albumin-stabilized nanoparticle, paclitaxel poliglumex, pamidronate, panitumumab, peginterferon alfa, pegaspargase, phenoxodiol, poly(I)-poly(C12U), procarbazine, ranpirimase, rebimastat, recombinant quadrivalent HPV vaccine, squalamine, staurosporine, STn-KLH vaccine, T4 endonuclease V, tazartene, 6,6',7,12-tetramethoxy-2,2'-dimethyl-1β-berbaman, thalidomide, TNFerade™, <sup>131</sup>I-tositumomab, trabectedin, triazone, tumor necrosis factor, Ukrain™, vaccinia-MUC-1 vaccine, L-valine-L-boroproline, Vitaxin™, vitespen, zoledronic acid and zorubicin.

In one embodiment, a composition comprising (or prepared using as API) one or more crystalline forms of Compound 1 (including crystalline salts) is administered in a therapeutically effective amount to a subject in need thereof to treat a disease during which is overexpressed one or more of antiapoptotic Bcl-2 protein, antiapoptotic Bcl-X<sub>L</sub> protein and antiapoptotic Bcl-w protein.

In another embodiment, a composition comprising (or prepared using as API) one or more crystalline forms of Compound 1 (including crystalline salts) is administered in a therapeutically effective amount to a subject in need thereof to treat a disease of abnormal cell growth and/or dysregulated apoptosis.

Examples of such diseases include, but are not limited to, cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer

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of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma or a combination thereof.

In a more particular embodiment, a composition comprising (or prepared using as API) one or more crystalline forms of Compound 1 (including crystalline salts) is administered in a therapeutically effective amount to a subject in need thereof to treat bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer or spleen cancer.

According to any of these embodiments, the composition is administered in combination therapy with one or more additional therapeutic agents.

For example, a method for treating mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma or a combination thereof in a subject comprises administering to the subject therapeutically effective amounts of (a) a composition comprising (or prepared using as API) crystalline Compound 1 free base and (b) one or more of etoposide, vincristine, CHOP, rituximab, rapamycin, R-CHOP, RCVP, DA-EPOCH-R or bortezomib.

In particular embodiments, a composition comprising (or prepared using as API) crystalline Compound 1 free base is administered in a therapeutically effective amount to a subject in need thereof in combination therapy with etoposide, vincristine, CHOP, rituximab, rapamycin, R-CHOP, RCVP, DA-EPOCH-R or bortezomib in a therapeutically effective amount, for treatment of a lymphoid malignancy such as B-cell lymphoma or non-Hodgkin's lymphoma.

In another embodiment, a composition of the invention is administered in a therapeutically effective amount to a subject in need thereof to treat an immune or autoimmune disorder. Such disorders include acquired immunodeficiency disease syndrome (AIDS), autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, thrombocytopenia, acute and chronic immune diseases associated with organ transplantation, Addison's disease, allergic diseases, alopecia, alopecia areata, atheromatous disease/arte-

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riosclerosis, atherosclerosis, arthritis (including osteoarthritis, juvenile chronic arthritis, septic arthritis, Lyme arthritis, psoriatic arthritis and reactive arthritis), autoimmune bullous disease, abetalipoproteinemia, acquired immunodeficiency-related diseases, acute immune disease associated with organ transplantation, acquired acrocyanosis, acute and chronic parasitic or infectious processes, acute pancreatitis, acute renal failure, acute rheumatic fever, acute transverse myelitis, adenocarcinomas, aerial ectopic beats, adult (acute) respiratory distress syndrome, AIDS dementia complex, alcoholic cirrhosis, alcohol-induced liver injury, alcohol-induced hepatitis, allergic conjunctivitis, allergic contact dermatitis, allergic rhinitis, allergy and asthma, allograft rejection, alpha-1-antitrypsin deficiency, Alzheimer's disease, amyotrophic lateral sclerosis, anemia, angina pectoris, ankylosing spondylitis-associated lung disease, anterior horn cell degeneration, antibody mediated cytotoxicity, antiphospholipid syndrome, anti-receptor hypersensitivity reactions, aortic and peripheral aneurysms, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, arthropathy, asthenia, asthma, ataxia, atopic allergy, atrial fibrillation (sustained or paroxysmal), atrial flutter, atrioventricular block, atrophic autoimmune hypothyroidism, autoimmune haemolytic anaemia, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), autoimmune mediated hypoglycemia, autoimmune neutropenia, autoimmune thrombocytopenia, autoimmune thyroid disease, B-cell lymphoma, bone graft rejection, bone marrow transplant (BMT) rejection, bronchiolitis obliterans, bundle branch block, burns, cachexia, cardiac arrhythmias, cardiac stun syndrome, cardiac tumors, cardiomyopathy, cardiopulmonary bypass inflammation response, cartilage transplant rejection, cerebellar cortical degenerations, cerebellar disorders, chaotic or multifocal atrial tachycardia, chemotherapy-associated disorders, chlamydia, choleosatis, chronic alcoholism, chronic active hepatitis, chronic fatigue syndrome, chronic immune disease associated with organ transplantation, chronic eosinophilic pneumonia, chronic inflammatory pathologies, chronic mucocutaneous candidiasis, chronic obstructive pulmonary disease (COPD), chronic salicylate intoxication, colorectal common varied immunodeficiency (common variable hypogammaglobulinemia), conjunctivitis, connective tissue disease-associated interstitial lung disease, contact dermatitis, Coombs-positive hemolytic anemia, cor pulmonale, Creutzfeldt-Jakob disease, cryptogenic autoimmune hepatitis, cryptogenic fibrosing alveolitis, culture-negative sepsis, cystic fibrosis, cytokine therapy-associated disorders, Crohn's disease, dementia pugilistica, demyelinating diseases, dengue hemorrhagic fever, dermatitis, dermatitis scleroderma, dermatologic conditions, dermatomyositis/polymyositis-associated lung disease, diabetes, diabetic arteriosclerotic disease, diabetes mellitus, diffuse Lewy body disease, dilated cardiomyopathy, dilated congestive cardiomyopathy, discoid lupus erythematosus, disorders of the basal ganglia, disseminated intravascular coagulation, Down's Syndrome in middle age, drug-induced interstitial lung disease, drug-induced hepatitis, drug-induced movement disorders induced by drugs which block CNS dopamine receptors, drug sensitivity, eczema, encephalomyelitis, endocarditis, endocrinopathy, enteropathic synovitis, epiglottitis, Epstein-Barr virus infection, erythromelalgia, extrapyramidal and cerebellar disorders, familial hemophagocytic lymphohistiocytosis, fetal thymus implant rejection, Friedreich's ataxia, functional peripheral arterial disorders, female infertility, fibrosis, fibrotic lung disease, fungal sepsis, gas gangrene, gastric ulcer, giant cell arteritis, glomerular nephritis, glomerulonephritides, Goodpasture's syndrome,



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goitrous autoimmune hypothyroidism (Hashimoto's disease), gouty arthritis, graft rejection of any organ or tissue, graft versus host disease, gram-negative sepsis, gram-positive sepsis, granulomas due to intracellular organisms, group B streptococci (GBS) infection, Graves' disease, hemosiderosis-associated lung disease, hairy cell leukemia, Haller-rorden-Spatz disease, Hashimoto's thyroiditis, hay fever, heart transplant rejection, hemachromatosis, hematopoietic malignancies (leukemia and lymphoma), hemolytic anemia, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, Henoch-Schoenlein purpura, hepatitis A, hepatitis B, hepatitis C, HIV infection/HIV neuropathy, Hodgkin's disease, hypoparathyroidism, Huntington's chorea, hyperkinetic movement disorders, hypersensitivity reactions, hypersensitivity pneumonitis, hyperthyroidism, hypokinetic movement disorders, hypothalamic-pituitary-adrenal axis evaluation, idiopathic Addison's disease, idiopathic leucopenia, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia, idiosyncratic liver disease, infantile spinal muscular atrophy, infectious diseases, inflammation of the aorta, inflammatory bowel disease, insulin dependent diabetes mellitus, interstitial pneumonitis, iridocyclitis/uveitis/optic neuritis, ischemia-reperfusion injury, ischemic stroke, juvenile pernicious anemia, juvenile rheumatoid arthritis, juvenile spinal muscular atrophy, Kaposi's sarcoma, Kawasaki's disease, kidney transplant rejection, legionella, leishmaniasis, leprosy, lesions of the corticospinal system, linear IgA disease, lipidema, liver transplant rejection, Lyme disease, lymphedema, lymphocytic infiltrative lung disease, malaria, male infertility idiopathic or NOS, malignant histiocytosis, malignant melanoma, meningitis, meningococemia, microscopic vasculitis of the kidneys, migraine headache, mitochondrial multisystem disorder, mixed connective tissue disease, mixed connective tissue disease-associated lung disease, monoclonal gammopathy, multiple myeloma, multiple systems degenerations (Mencel, Dejerine-Thomas, Shy-Drager and Machado-Joseph), myalgic encephalitis/Royal Free Disease, myasthenia gravis, microscopic vasculitis of the kidneys, mycobacterium avium intracellulare, mycobacterium tuberculosis, myelodysplastic syndrome, myocardial infarction, myocardial ischemic disorders, nasopharyngeal carcinoma, neonatal chronic lung disease, nephritis, nephrosis, nephrotic syndrome, neurodegenerative diseases, neurogenic I muscular atrophies, neutropenic fever, non-alcoholic steatohepatitis, occlusion of the abdominal aorta and its branches, occlusive arterial disorders, organ transplant rejection, orchitis/epididymitis, orchitis/vasectomy reversal procedures, organomegaly, osteoarthritis, osteoporosis, ovarian failure, pancreas transplant rejection, parasitic diseases, parathyroid transplant rejection, Parkinson's disease, pelvic inflammatory disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, perennial rhinitis, pericardial disease, peripheral atherosclerotic disease, peripheral vascular disorders, peritonitis, pernicious anemia, phacogenic uveitis, pneumocystis carinii pneumonia, pneumonia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), post-perfusion syndrome, post-pump syndrome, post-MI cardiomyopathy syndrome, postinfectious interstitial lung disease, premature ovarian failure, primary biliary cirrhosis, primary sclerosing hepatitis, primary myxoedema, primary pulmonary hypertension, primary sclerosing cholangitis, primary vasculitis, progressive supranuclear palsy, psoriasis, psoriasis type 1, psoriasis type 2, psoriatic arthropathy, pulmonary hypertension secondary to connective tissue disease, pulmonary manifestation of polyarteritis nodosa, post-inflammatory interstitial lung disease, radiation fibrosis, radiation

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therapy, Raynaud's phenomenon and disease, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, Reiter's disease, renal disease NOS, renovascular hypertension, reperfusion injury, restrictive cardiomyopathy, rheumatoid arthritis-associated interstitial lung disease, rheumatoid spondylitis, sarcoidosis, Schmidt's syndrome, scleroderma, senile chorea, senile dementia of Lewy body type, sepsis syndrome, septic shock, seronegative arthropathies, shock, sickle cell anemia, Sjögren's disease-associated lung disease, Sjögren's syndrome, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, sperm autoimmunity, multiple sclerosis (all subtypes), spinal ataxia, spinocerebellar degenerations, spondyloarthropathy, sporadic polyglandular deficiency type I, sporadic polyglandular deficiency type II, Still's disease, streptococcal myositis, stroke, structural lesions of the cerebellum, subacute sclerosing panencephalitis, sympathetic ophthalmia, syncope, syphilis of the cardiovascular system, systemic anaphylaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic lupus erythematosus-associated lung disease, systemic sclerosis, systemic sclerosis-associated interstitial lung disease, T-cell or FAB ALL, Takayasu's disease/arteritis, telangiectasia, Th2-type and Th1-type mediated diseases, thromboangitis obliterans, thrombocytopenia, thyroiditis, toxicity, toxic shock syndrome, transplants, trauma/hemorrhage, type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), type B insulin resistance with acanthosis nigricans, type III hypersensitivity reactions, type IV hypersensitivity, ulcerative colitic arthropathy, ulcerative colitis, unstable angina, uremia, urosepsis, urticaria, uveitis, valvular heart diseases, varicose veins, vasculitis, vasculitic diffuse lung disease, venous diseases, venous thrombosis, ventricular fibrillation, vitiligo acute liver disease, viral and fungal infections, vital encephalitis/aseptic meningitis, vital-associated hemaphagocytic syndrome, Wegener's granulomatosis, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, yersinia and salmonella-associated arthropathy and the like.

The present invention also provides a method for maintaining in bloodstream of a human cancer patient a therapeutically effective plasma concentration of Compound 1 and/or one or more metabolites thereof, comprising administering to the subject a pharmaceutical composition as described herein, in a dosage amount equivalent to about 50 to about 500 mg Compound 1 per day, at an average dosage interval of about 3 hours to about 7 days.

What constitutes a therapeutically effective plasma concentration depends inter alia on the particular cancer present in the patient, the stage, severity and aggressiveness of the cancer, and the outcome sought (e.g., stabilization, reduction in tumor growth, tumor shrinkage, reduced risk of metastasis, etc.). It is strongly preferred that, while the plasma concentration is sufficient to provide benefit in terms of treating the cancer, it should not be sufficient to provoke an adverse side-effect to an unacceptable or intolerable degree.

For treatment of cancer in general and of a lymphoid malignancy such as non-Hodgkin's lymphoma in particular, the plasma concentration of Compound 1 should in most cases be maintained in a range of about 0.5 to about 10  $\mu\text{g/ml}$ . Thus, during a course of Compound 1 therapy, the steady-state  $C_{\text{max}}$  should in general not exceed about 10  $\mu\text{g/ml}$ , and the steady-state  $C_{\text{min}}$  should in general not fall below about 0.5  $\mu\text{g/ml}$ . It will further be found desirable to select, within the ranges provided above, a daily dosage amount and average dosage interval effective to provide a  $C_{\text{max}}/C_{\text{min}}$  ratio not greater than about 5, for example not greater than about 3, at steady-state.



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It will be understood that longer dosage intervals will tend to result in greater  $C_{max}/C_{min}$  ratios. Illustratively, at steady-state, an Compound 1  $C_{max}$  of about 3 to about 8  $\mu\text{g}/\text{ml}$  and  $C_{min}$  of about 1 to about 5  $\mu\text{g}/\text{ml}$  can be targeted by the present method.

A daily dosage amount effective to maintain a therapeutically effective Compound 1 plasma level is, according to the present embodiment, about 50 to about 1000 mg. In most cases a suitable daily dosage amount is about 200 to about 400 mg. Illustratively, the daily dosage amount can be for example about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 750 or about 1000 mg.

An average dosage interval effective to maintain a therapeutically effective Compound 1 plasma level is, according to the present embodiment, about 3 hours to about 7 days. In most cases, a suitable average dosage interval is about 8 hours to about 3 days, or about 12 hours to about 2 days. A once-daily (q.d.) administration regimen is often suitable.

As in other embodiments, administration according to the present embodiment can be with or without food, i.e., in a non-fasting or fasting condition. It is generally preferred to administer the present compositions to a non-fasting patient.

When introducing elements of the present disclosure or the preferred embodiments(s) thereof, the articles “a”, “an”, “the” and “said” are intended to mean that there are one or more of the elements. The terms “comprising”, “including”

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and “having” are intended to be inclusive and mean that there may be additional elements other than the listed elements.

As various changes could be made in the above described methods and/or compositions without departing from the scope of the disclosure, it is intended that all matter contained in the above description and shown in the accompanying figures shall be interpreted as illustrative and not be viewed in a limiting sense.

What is claimed is:

1. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethyl-cyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide (Compound 1) in a crystalline form wherein the crystalline form is Compound 1 free base anhydrate, characterized by a powder X-ray diffraction pattern having five or more peaks selected from those at 6.3, 7.1, 9.0, 9.5, 12.5, 14.5, 14.7, 15.9, 16.9, and 18.9 degrees  $2\theta$  (pattern A), each peak being  $\pm 0.2$  degrees  $2\theta$ , when measured at about 25° C. with Cu  $K_{\alpha}$  radiation at 1.54178 Å.

2. A pharmaceutical composition comprising the compound in said crystalline form of claim 1 and one or more pharmaceutically acceptable excipients.

3. A process for preparing a pharmaceutical solution comprising dissolving the compound in said crystalline form of claim 1 in a pharmaceutically acceptable solvent or mixture of solvents.

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